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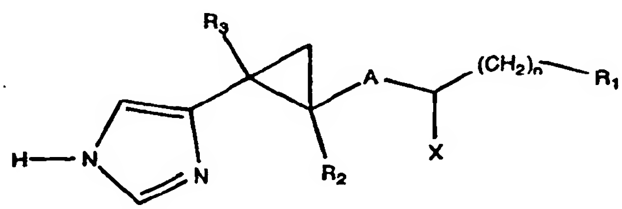
(54) Title: 2-(1H-4(5)-IMIDAZOYL) CYCLOPROPYL DERIVATIVES

(57) Abstract



(1.0)

(a)

(b)

The present invention provides compounds having H_3 histamine receptor antagonist activity of general formula (1.0), wherein R_2 is a hydrogen or a methyl or ethyl group; R_3 is a hydrogen or a methyl or ethyl group; n is 0, 1, 2, 3, 4, 5, or 6; and R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (c) alkyl; (d) heterocyclic; (e) decahydronaphthalene; and (f) octahydroindene; with the provisos that when X is H, A can be $-CH_2CH_2-$, $-COCH_2-$, -CONH-, $-CON(CH_3)-$, -CH=CH-, α, $-CH_2-NH-$, $-CH_2-N(CH_3)-$, $-CH(OH)CH_2-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-CH_2O-$, $-CH_2S-$, and -NHCOO-; when X is NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, CH_3, SH and SCH_3; A can be -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or β; and when R_1 and X taken together denote a 5,6 or 6,6 saturated bicyclic ring structure, X can be NH, O, or S. The pharmaceutically acceptable salts, hydrates, and individual stereoisomers of compounds of structral formula (1.0), as well as mixtures thereof, are also contemplated as falling within the scope of the present invention. This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with an effective amount of a compound of said formula and a method of treating conditions in which antagonism of histamine H_3 receptors may be of therapeutic importance.

2-(1H-4(5)-IMIDAZOYL) CYCLOPROPYL DERIVATIVES

TECHNICAL FIELD

This invention relates to compounds having pharmacological activity, to compositions containing these compounds, and to a method of treatment employing the compounds and compositions. More particularly, this invention concerns certain 2-(1H-4(5)-imidazoyl) cyclopropyl derivatives and their salts or solvates. These compounds have H_3 histamine receptor antagonist activity. This invention also relates to pharmaceutical compositions containing these compounds, and to a method of treating disorders in which histamine H_3 receptor blockade is beneficial.

BACKGROUND OF THE INVENTION

Histamine is a chemical messenger involved in various complex biological actions. When released, histamine interacts with specific macromolecular receptors on the cell surface or within a target cell to elicit changes in many different bodily functions. Various cell types including smooth muscle, blood cells, cells of the immune system, endocrine and exocrine cells as well as neurons respond to histamine by stimulating the formation of intracellular signals, including formation of phosphatidylinositol or adenylate cyclase. Evidence that histamine plays a role as a neurotransmitter was established by the mid to late 1970's (Schwartz, 1975) *Life Sci.* 17: 503-518. Immunohistochemical studies identified histaminergic cell bodies in the tuberomammillary nucleus of the posterior hypothalamus with widespread projections in the dicencephalon and telencephalon (Inagaki et al., 1988) *J. Comp. Neurol.* 273: 283-300.

Identification of two histamine receptors (H_1 and H_2) was reported to mediate the biochemical actions of histamine on neurons . Recently, studies have demonstrated the existence of a third subtype of histamine receptor, the histamine H_3 receptor (Schwartz et al., 1986) *TIPS* 8: 24-28. Various studies have now demonstrated that histamine H_3 receptors are found on the histaminergic nerve terminals in the brains of several species, including man (Arrang et al., 1983) *Nature* 302: 832-837. The H_3 receptor found on the histaminergic nerve terminal was defined as an autoreceptor and could intimately control the amount of histamine released from the neurons. Histamine, the natural compound, was capable of stimulating this autoreceptor but when tested against known H_1 and H_2 receptor agonists and antagonists, a distinct pharmacological profile emerged. Further, H_3 receptors have been identified on cholinergic, serotoninergic and monoamine nerve terminals in the

peripheral nervous system (PNS) and central nervous system including the cerebral cortex and cerebral vessels. These observations suggest that H_3 receptors are uniquely located to modulate histamine as well as other neurotransmitter release, and H_3 antagonists could be important mediators of neuronal activity.

As stated, CNS histaminergic cell bodies are found in the magnocellular nuclei of the hypothalamic mammillary region and these neurons project diffusely to large areas of the forebrain. The presence of histaminergic cell bodies in the tuberomamillary nucleus of the posterior hypothalamus, a brain area involved in the maintenance of wakefulness, and their projections to the cerebral cortex suggest a role in modulating the arousal state or sleep-wake. The histaminergic projection to many limbic structures such as the hippocampal formation and the amygdaloid complex suggest roles in functions such as autonomic regulation, control of emotions and motivated behaviors, and memory processes.

The concept that histamine is important for the state of arousal, as suggested by the location of histaminergic pathways, is supported by other types of evidence. Lesions of the posterior hypothalamus is well known to produce sleep. Neurochemical and electrophysiological studies have also indicated that the activity of histaminergic neurons is maximal during periods of wakefulness and is suppressed by barbiturates and other hypnotics. Intraventricular histamine induces the appearances of an arousal EEG pattern in rabbits and increased spontaneous locomotor activity, grooming and exploratory behavior in both saline and pentobarbital-treated rats.

In contrast, a highly selective inhibitor of histidine decarboxylase, the sole enzyme responsible for histamine synthesis, has been shown to impair waking in rats. These data support the hypothesis that histamine may function in modulating behavioral arousal. The role of the H_3 receptor in sleep-waking parameters has been recently demonstrated (Lin et al., 1990) *Brain Res.* 529: 325-330. Oral administration of RAMHA, a H_3 agonist, caused a significant increase in deep slow wave sleep in the cat. Conversely, thioperamide, a H_3 antagonist, enhanced wakefulness in a dose-dependent fashion. Thioperamide has also been shown to increase wakefulness and decrease slow wave and REM sleep in rats. These findings are consistent with in vivo studies demonstrating that thioperamide caused an increase in synthesis and release of histamine. Together, these data demonstrate that selective H_3 antagonists may be useful in the treatment of arousal states and sleep disorders.

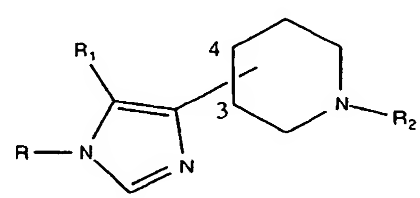
Serotonin, histamine, and acetylcholine have all been demonstrated to be diminished in the Alzheimer's (AD) brain. The histamine H_3 receptor has been demonstrated to regulate the release of each of these neurotransmitters. An H_3 receptor antagonist would

therefore be expected to increase the release of these neurotransmitters in brain. Since histamine has been demonstrated to be important in arousal and vigilance, H_3 receptor antagonists might enhance arousal and vigilance via increasing levels of neurotransmitter release and improve cognition. Thus, the use of H_3 receptor antagonists in AD, attention deficit hyperactive disorders (ADHD), age-related memory dysfunction and other cognitive disorders would be supported.

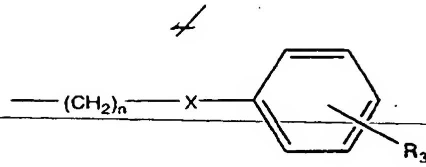
H_3 receptor antagonists may be useful in treating several other CNS disorders. It has been suggested that histamine may be involved in the control of sleep/wake states as well as states of arousal and alertness, cerebral circulation, energy metabolism, and hypothalmic hormone secretion. Recent evidence has indicated the possible use of H_3 antagonists in the treatment of epilepsy. Work has demonstrated an inverse correlation between the duration of clonic convulsions and brain histamine levels. Thioperamide, a H_3 antagonist, was also shown to significantly and dose-dependently decrease the durations of every convulsive phase after electrically-induced convulsions and increase the electroconvulsive threshold.

In spite of their low density, H_3 receptor binding sites can be detected outside the brain. Several studies have revealed the presence of H_3 heteroreceptors in the gastrointestinal tract, as well as upon neurons of the respiratory tract. Accordingly, an H_3 receptor antagonist may be useful in the treatment of diseases and conditions such as asthma, rhinitis, airway congestion, inflammation, hyper and hypo motility and acid secretion of the gastrointestinal tract. Peripheral or central blockade of H_3 receptors may also contribute to changes in blood pressure, heart rate and cardiovascular output and could be used in the treatment of cardiovascular diseases.

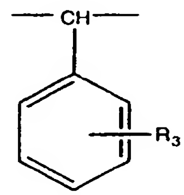
US 4,707,487 discloses compounds of the general formula:



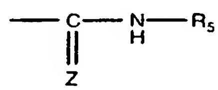
in which R_1 denotes H, CH_3, or C_2H_5, R denotes H or R_2 and R_2 denotes an alkyl, piperonyl, 3-(1-benzimidazolonyl)-propyl group; a group of formula:



in which n is 0, 1, 2, or 3, X is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or

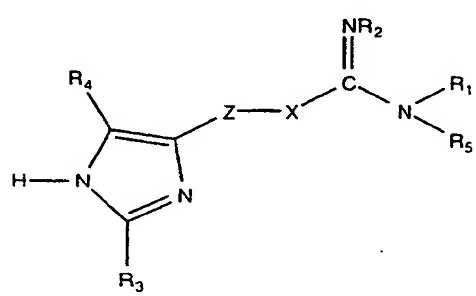


and R_3 is H, CH_3, F, CN or an acyl group; or alternatively a group of formula:

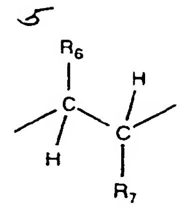


in which Z denotes an O or S atom or a divalent group NH, N-CH_3, or N-CN, and R_5 denotes an alkyl group, a cycloalkyl group which can bear a phenyl substituent, a phenyl group which can bear a CH_3 or F substituent, a phenylalkyl (C_1-C_3) group or a naphthyl, adamantyl, or p-toluenesulphonylgroup. It is also disclosed that these compounds antagonize the histamine H_3 receptors and increase the rate of renewal of cerebral histamine.

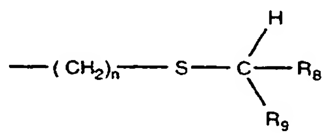
WO 92/15567 discloses compounds of general formula:



wherein: Z is a group of formula $(CH_2)_m$, wherein m = 1-5 or a group of the formula:

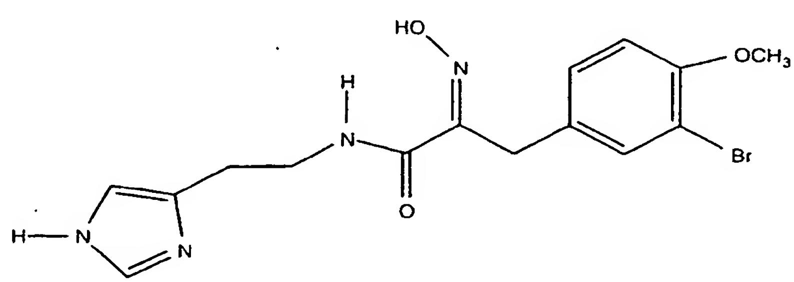


wherein R6= (C_1-C_3) alkyl, R7 = (C_1-C_3) alkyl; X represents S, NH, or CH_2; R_1 represents hydrogen, (C_1-C_3) alkyl-, aryl (C_1-C_{10}) alkyl-, wherein aryl may optionally be substituted, aryl, (C_5-C_7) cycloalkyl, (C_1-C_{10}) alkyl-, or a group of the formula:



wherein n = 1-4, R_8 is aryl, aryl (C_1-C_{10}) alkyl-, (C_5-C_7) cycloalkyl- or (C_5-C_7) cycloalkyl (C_1-C_{10}) alkyl-, and R_9 is hydrogen, (C_1-C_{10}) alkyl- or aryl; R_2 and R_5 represent hydrogen, (C_1-C_3) alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; R_3 represents hydrogen, (C_1-C_3) alkyl, aryl, or arylalkyl-, wherein aryl may be substituted; and R_4 represents hydrogen, amino-, nitro-, cyano-, halogen-, (C_1-C_3) alkyl, aryl, or arylalkyl-, wherein aryl may optionally be substituted; wherein aryl is phenyl, substituted phenyl, naphthyl, substituted naphthyl, pyridyl or substituted pyridyl. These compounds are reported to have agonistic or antagonistic activity on the histamine H_3 receptor.

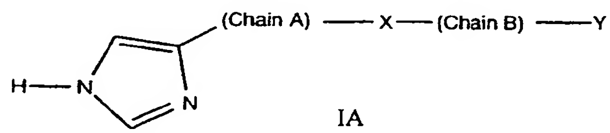
US 5,217,986 discloses compound of formula:



This compound is reported to be active in an H_3 receptor assay, is reported to be an H_3 antagonist on guinea pig ileum, and accordingly is said to be useful in the treatment of diseases and conditions such as asthma, rhinitis, airway congestion, inflammation, cardiac arrhythmias, hypertension, hyper and hypo motility and acid secretion of the

gastrointestinal tract, hypo and hyper-activity of the central nervous system, migraine, and glaucoma.

WO 93/14070 discloses compounds of general formula:



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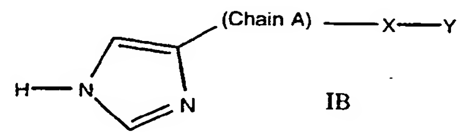

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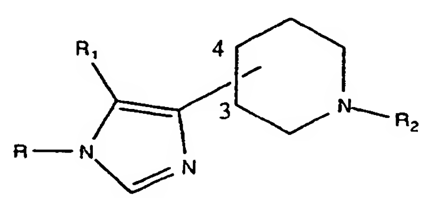
Chain A represents a hydrocarbon chain, saturated or unsaturated, of 1-6 carbon atoms in length; X represents -O-, -S-, -NH-, -NHCO-, -N(alkyl)CO-, -NHCONH-, -NH-CS-NH-, -NHCS-,-O-CO-, -CO-O-, -OCONH-, -OCON(alkyl)-, -OCONH-CO-, -CONH-, -CON(alkyl)-, -SO-, -CO-,-CHOH-, -NR-C(=NR")-NR'-, R and R' can be hydrogen or alkyl and R" is hydrogen or cyano, or COY_1, Y_1 is alkoxy radical. Chain B represents an alkyl group $-(CH_2)_n-$, n = 0-5 or an alkylchain of 2-8 carbon atoms interrupted by an oxygen or sulfur atom or a group like $-(CH_2)_n$-O-or $-(CH_2)_n$-S- wherein n=1 or 2. Y represents $(C_1\text{-}C_8)$alkyl, $(C_3\text{-}C_6)$ cycloalkyl, bicycloalkyl, aryl, cycloalkenyl, heterocycle.

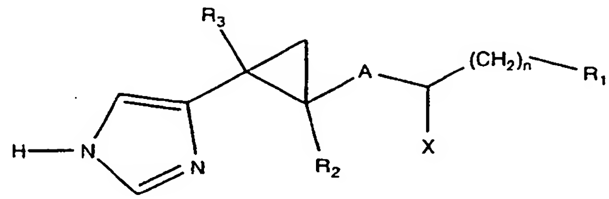
US 5,290,790 discloses compounds of the same general structure as US 4,707,487:



but specifically includes amides wherein R_2 is CO-NR'R" and R'R" are independently selected from the group consisting of (a) hydrogen; (b) phenyl or substituted phenyl; (c) alkyl; (d) cycloalkyl; and (e) alkylcycloalkyl such as cyclohexylmethyl or cyclopentylethyl.

SUMMARY OF THE INVENTION

The present invention provides, in its principal aspect, compounds of the general formula:



(1.0)

where R_2 is a hydrogen or a methyl or ethyl group;

R_3 is a hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (c) alkyl; (d) heterocyclic; (e) decahydronapthalene; and (f) octahydroindene;

with the provisos that

when X is H, A can be $-CH_2CH_2-$, $-COCH_2-$, -CONH-, $-CON(CH_3)-$, -CH=CH-, $-C\equiv C-$, $-CH_2-NH-$, $-CH_2-N(CH_3)-$, $-CH(OH)CH_2-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-CH_2O-$,$-CH_2S-$, or -NHCOO-;

when X is NH_2, $NH(CH_3)$,$N(CH_3)_2$, OH, OCH_3, CH_3, SH, or SCH_3; A can be -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$,$-CH(OH)CH_2-$, or $-C\equiv C-$; and

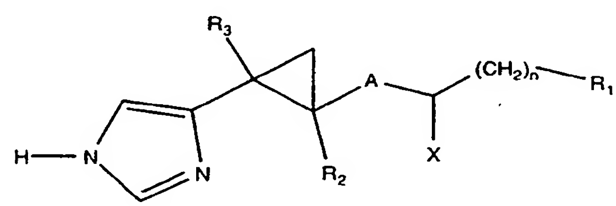
when R_1 and X taken together denote a 5,6 or 6,6 saturated bicyclic ring structure X can be NH, O, or S.

The pharmaceutically acceptable salts, hydrates and individual stereoisomers of compounds of structural formula (1.0) above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention.

This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier in combination with an effective amount of a compound of formula (1.0).

The present invention also provides a method of treating conditions in which antagonism of histamine H_3 receptors may be of therapeutic importance such as allergy, inflammation, cardiovascular disease (i.e. hyper or hypotension), gastrointestinal disorders (acid secretion, motility) and CNS disorders involving attention or cognitive disorders, (i.e., Alzheimer's, Attention Deficit Hyperactive Disorder, age-related memory dysfunction, stroke, etc), psychiatric and motor disorders (i.e., depression, schizophrenia, obsessive-compulsive disorders, tourette's, etc.) and sleep disorders (i.e., narcolepsy, sleep apnea, insomnia, disturbed biological and circadian rhythms, hyper and hyposomnolence, and related sleep disorders), epilepsy, hypothalamic dysfunction (i.e., eating disorders such as obesity, anorexia/bulimia, thermoregulation, hormone release) comprising administering an effective amount of a compound of formula (1.0) to a patient in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION



(1.0)

Preferably for compounds of formula (1.0); the cyclopropane attended at the 4(5)-position of the imidazole ring has the trans configuration and

when X is H, A can be $-CH_2CH_2-$, $-COCH_2-$, -CONH-, $-CON(CH_3)-$, -CH=CH-, $-C\equiv C-$, $-CH_2-NH-$, $-CH_2-N(CH_3)-$, $-CH(OH)CH_2-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-CH_2O-$,$-CH_2S-$, or -NHCOO-;

R_2 is a hydrogen or a methyl or ethyl group;

R_3 is a hydrogen or a methyl or ethyl group;

n is 0, 1, 2, 3, 4, 5, or 6; and

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (c) alkyl; (d) heterocyclic; (e) decahydronapthalene; and (f) octahydroindene;

when X is NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, CH_3, SH, and SCH_3; A can be -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-,

-$COCH_2$-, -CH_2CH_2-,-$CH(OH)CH_2$-, or —C≡C— ;

R_2 is a hydrogen or a methyl or ethyl group;

R_3 is a hydrogen or a methyl or ethyl group;

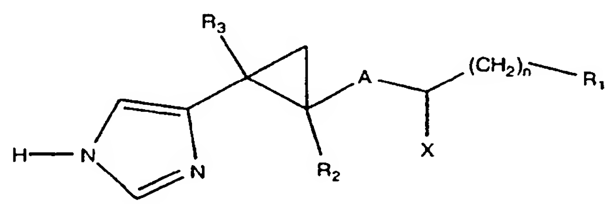
n is 0, 1, 2, 3, 4, 5, or 6;

R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (c) alkyl; (d) heterocyclic; (e) decahydronapthalene; and (f) octahydroindene;

when R_1 and X taken together denote a 5,6 or 6,6 saturated bicyclic ring structure X can be NH, O, or S; and

when X is constrained in a 5,6 or 6,6 saturated bicyclic ring structure, for example, when X=NH, R_1 and X taken together mean an octahydroindole ring structure directly attached to A.

More preferably, the present invention provides compounds of the general formula:



(1.0)

where A is -CONH, -CH=CH-, -NHCOO-, or —C≡C— ;

X is H or NH_2;

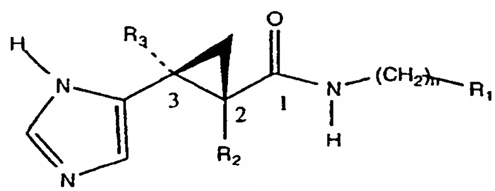
R_2 and R_3 are H;

n is 0, 1, 2 or 3;

R_1 is C_6 cyclohexyl, phenyl or substituted phenyl.

The pharmaceutically acceptable salts, hydrates and individual stereoisomers of compounds of structural formula (1.0) above, as well as mixtures thereof, are also contemplated as falling within the scope of the present invention.

Representative compounds of this invention include compounds of the formulae (2.0) through (51.0):



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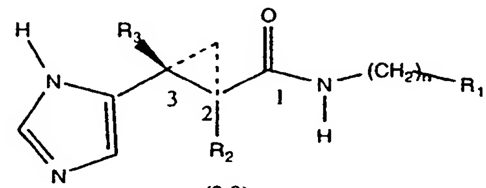

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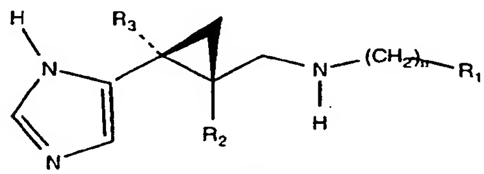

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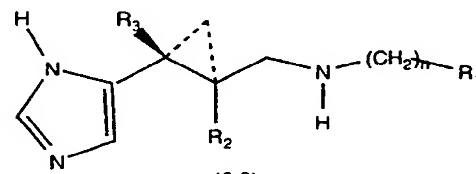

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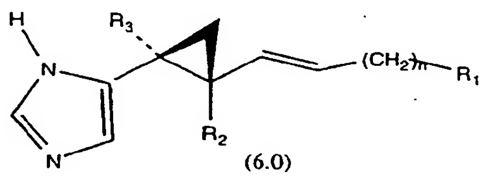

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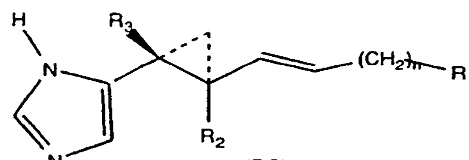

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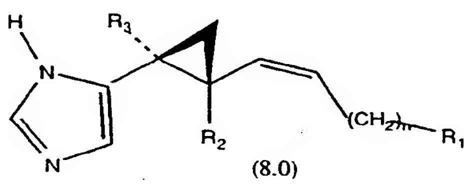

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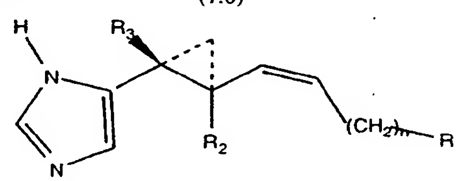

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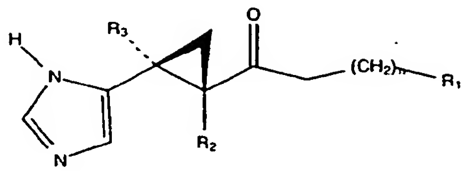

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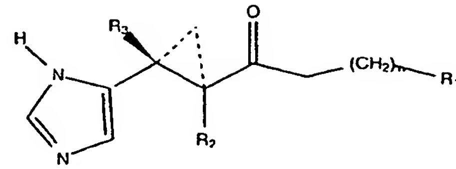

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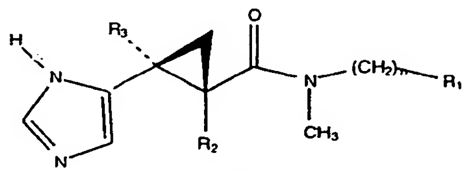

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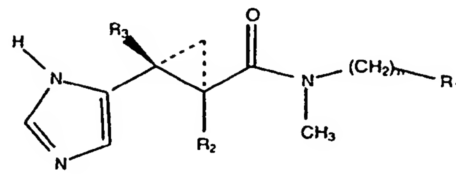

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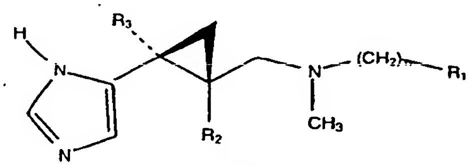

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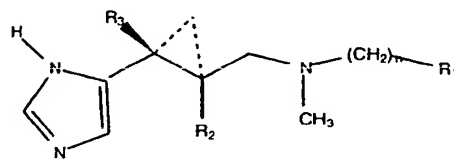

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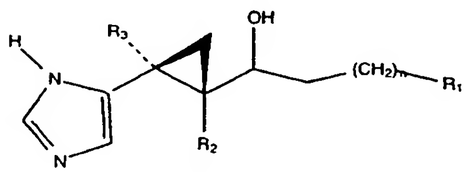

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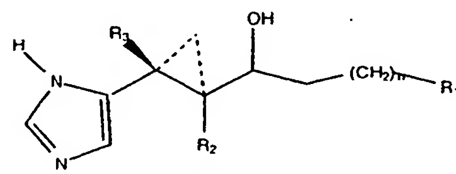

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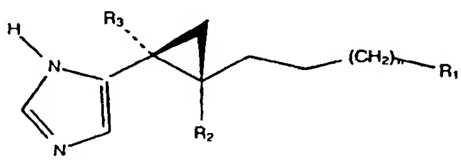

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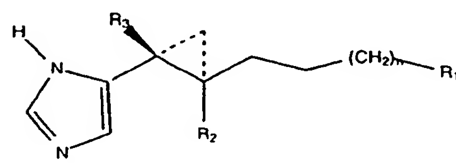

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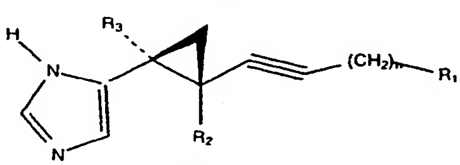

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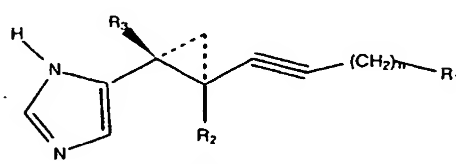

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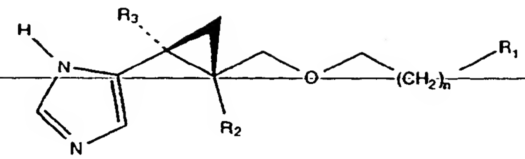

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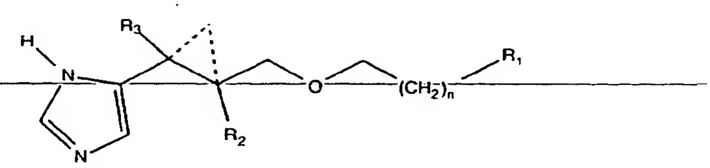

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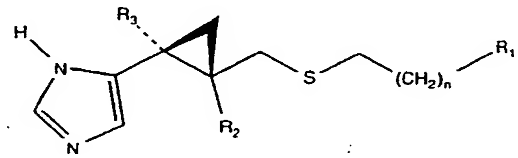

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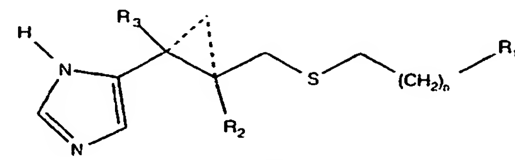

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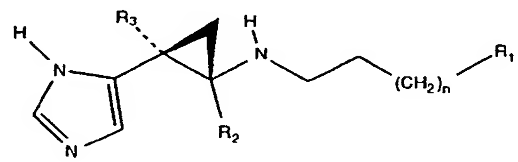

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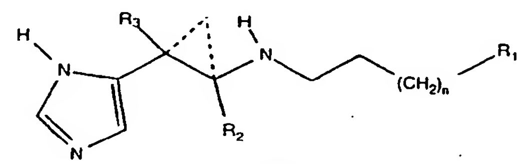

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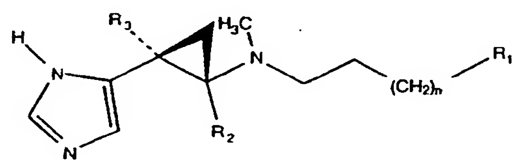

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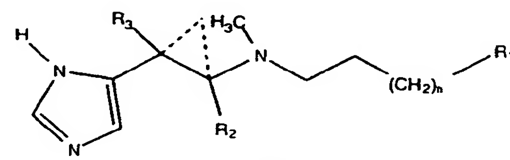

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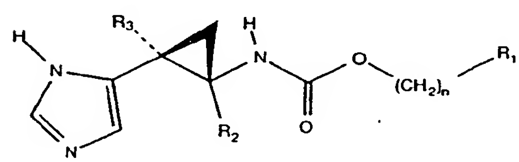

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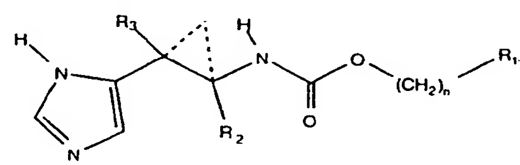

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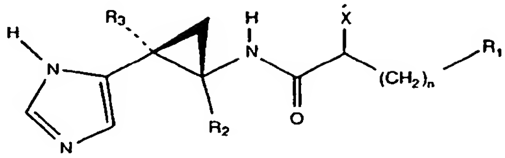
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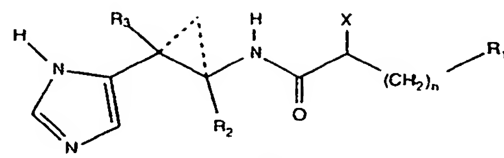
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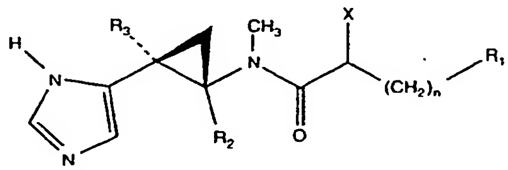
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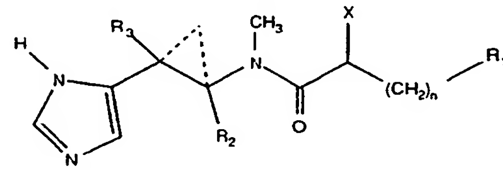
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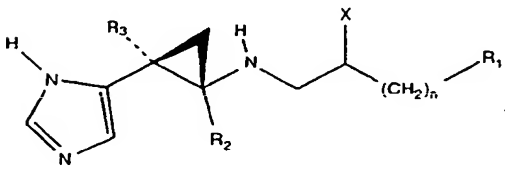
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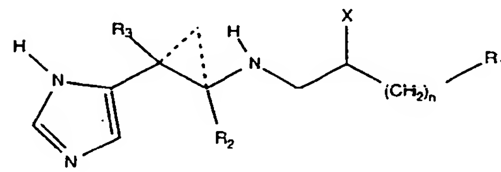
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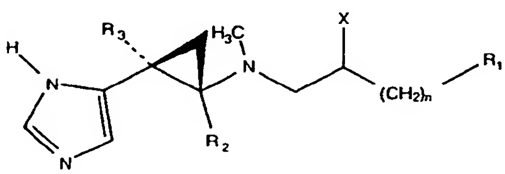
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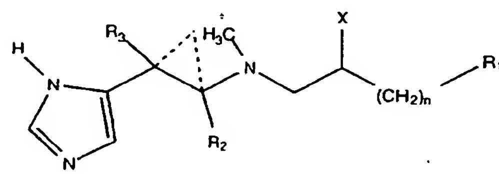
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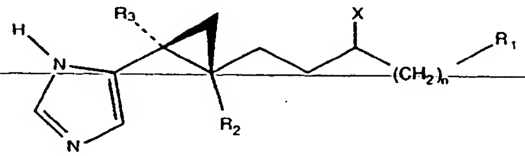

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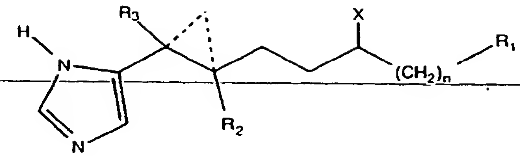

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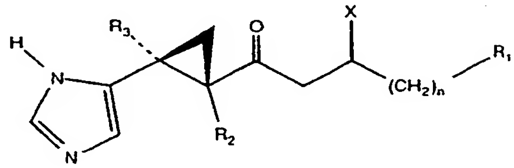

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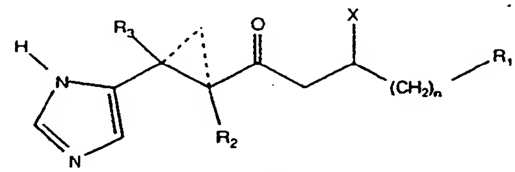

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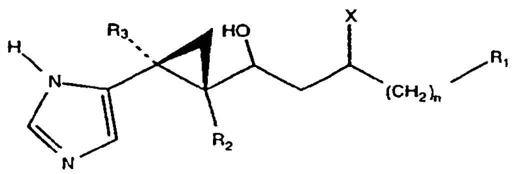

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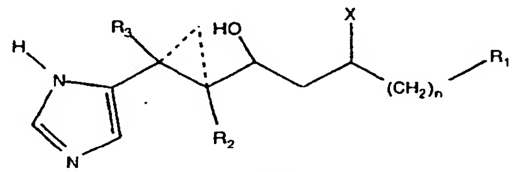

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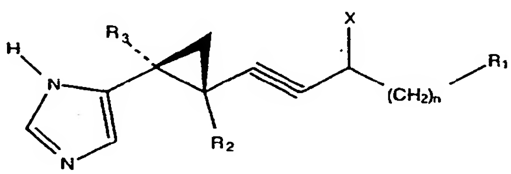

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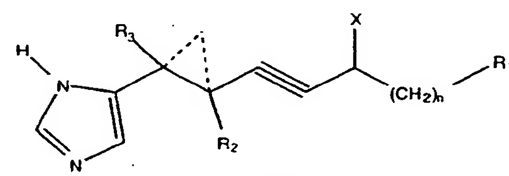

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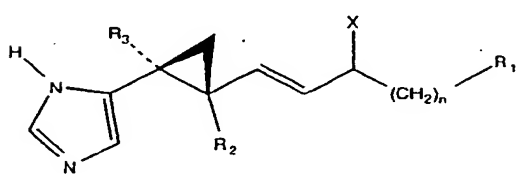

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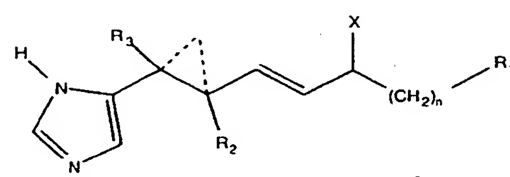

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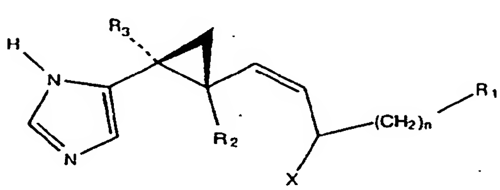

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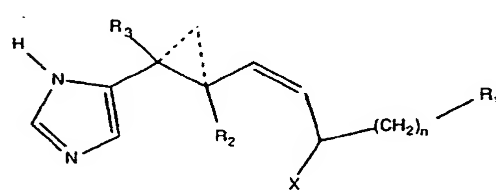

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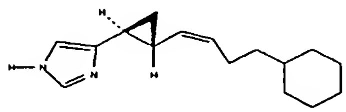
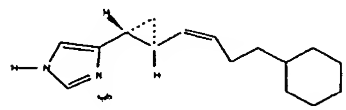
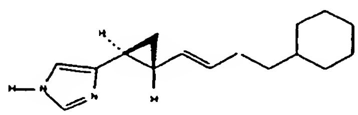
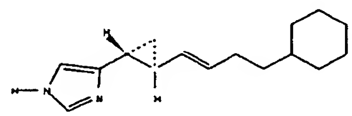
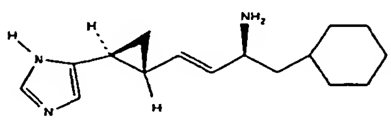
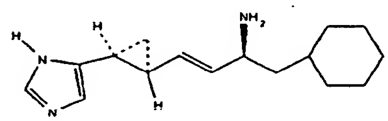
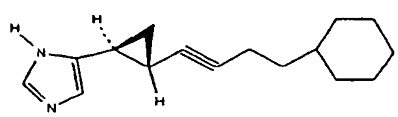
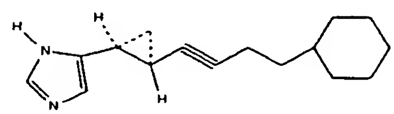
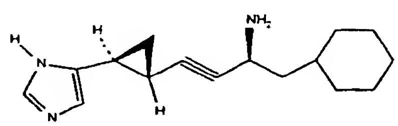
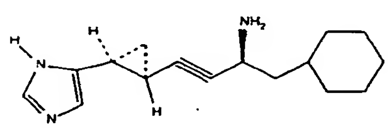
Particularly preferred compounds of the present invention include

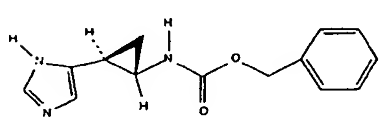
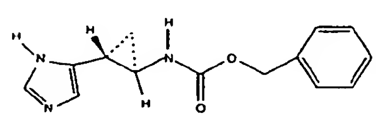
 

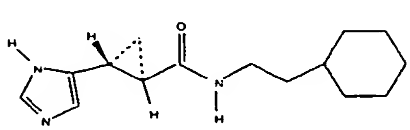
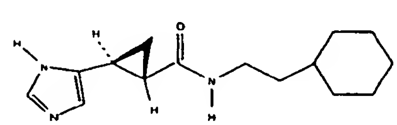
 

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of formula (1.0) can exist in unhydraated as well as hydrated forms, e.g., hemi-hydrate, mono-, tetra-, decahydrates, etc. The water may be removed by

heating or other means to form the anhydrous compound. In general, the hydrated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like are equivalent to the unhydrated forms for the purposes of the invention.

Certain compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the nitrogen atoms may form salts with acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous hydroxide, potassium carbonate, ammonia, and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid salts are equivalent to their respective free base forms for purposes of the invention. (See, for example S.M. Berge, et al.,"Pharmaceutical Salts," *J. Pharm. Sci.*, 66: 1-19 (1977) which is incorporated herein by reference.

As throughout this specification and appended claims, the following terms have the meanings ascribed to them:

The term "alkyl" as used herein refers to straight or branched chain radicals derived from saturated hydrocarbons by the removal of one hydrogen atom. Representative examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, and the like.

The term "heterocyclic" as used herein refers to a closed-ring structure in which one or more of the atoms in the ring is an element other than carbon. Representative heterocyclic groups are preferably saturated and include pyrrolidines, tetrahydrofuranes, tetrahydrothiophenes, tetrahydroisoquinolines and octahydroindole groups.

The term "substituted phenyl" as used herein refers to a phenyl group substituted by one or more groups such as alkyl, halogen, amino, methoxy, and cyano groups.

The term "bicyclic alkyl" as used herein refers to an organic compound having two ring structures connected to an alkyl group. They may or may not be the same type of ring and the rings may be substituted by one or more groups. Representative bicyclic alkyl groups include adamanthyl, decahydronaphthalene and norbornane.

Individual enantiomeric forms of compounds of the present invention can be separated from mixtures thereof by techniques well known in the art. For example, a mixture of diastereoisomeric salts may be formed by reacting the compounds of the present invention with an optically pure form of the acid, followed by purification of the mixture of diastereoisomers by recrystallization or chromatography and subsequent recovery of the resolved compound from the salt by basification. Alternatively, the optical isomers of the compounds of the present invention can be separated from one another by chromatographic techniques employing separation on an optically active chromatographic medium.

The present invention also provides pharmaceutical compositions which comprise one or more of the compounds of formula (1.0) above formulated together with one or more nontoxic pharmaceutically acceptable carriers. The pharmaceutical compositions may be specifically formulated for oral administration in solid or liquid form, parental injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, and topically in accordance with the present invention.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as perservatives, wetting agents and emulsifying agents.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form.

Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylccllulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hardfilled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredients(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum methydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

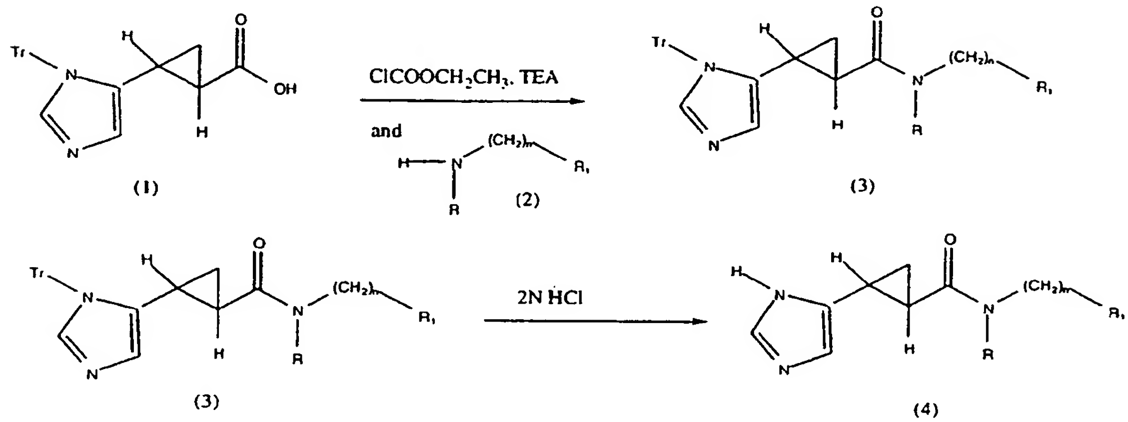
Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology,* Volume XIV, Academic Press, New York, N.Y. (1976) p.33 et seq.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of the invention.

The following processes and techniques may be employed to produce compounds of formula (1.0). The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will frequently necessitate judgement as to the order of synthetic steps, protecting groups required and deprotection conditions.

A. PREPARATION OF COMPOUNDS WHEREIN A IS -CONH- OR CON(CH_3) -

Scheme I

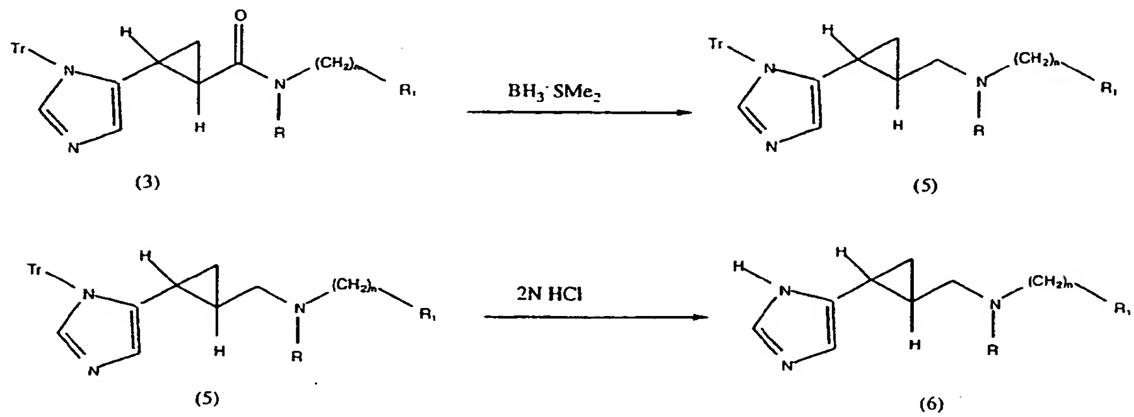


SCHEME I

According to the foregoing reaction scheme I, 3-(1-Triphenylmethyl-5-imidazoyl) cyclopropanecarboxylic acid (1), prepared as a racemic mixture of trans cyclopropanes using the method of Burger, et al., *J. Med. Chem.*, (1970), 13: 33-35, is converted to an activated ester through the action of ethyl chloroformate and triethylamine. The activated ester is reacted in situ with amine (2) to provide the 3-(1-Triphenylmethyl-5-imidazoyl)cyclopropanecarboxamide (3). The Trityl protecting group can be removed with acid, preferably aqueous 2N HCl, to give 3-(1H-5-imidazoyl)cyclopropanecarboxamide (4).

B. PREPARATION OF COMPOUNDS WHEREIN A IS $-CH_2NH-$ OR $-CH_2NCH_3-$

Scheme II

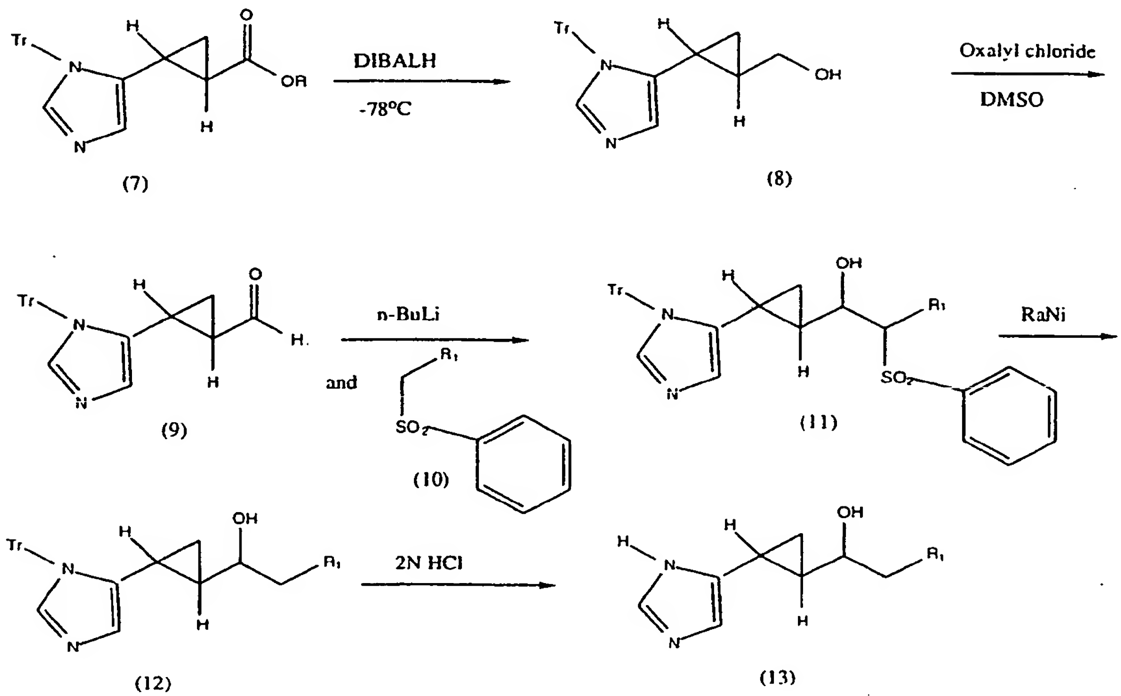


SCHEME II

According to the foregoing reaction scheme II, 3-(1-Triphenylmethyl-5-imidazoyl) cyclopropanecarboxamide (3), prepared as described in scheme I, is treated with excess borane-methyl sulfide complex to provide 1-(1-Triphenylmethyl-5-imidazoyl)cyclopropylamine (5). The Trityl protecting group is removed with aqueous 2N HCl to give 1-(1H-5-imidazoyl)cyclopropylamine (6).

C. PREPARATION OF COMPOUNDS WHEREIN A IS -CH(OH)CH_2-

Scheme III

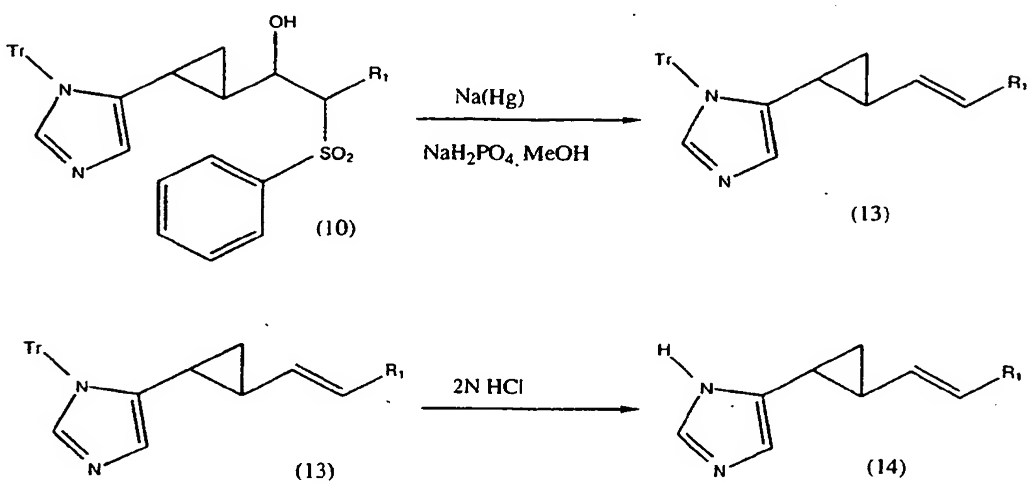


SCHEME III

According to the foregoing reaction scheme III, 3-(1-Triphenylmethyl-5-imidazoyl) cyclopropanecarboxylic acid ester (7) is treated with excess DIBALH at -78° C to provide alcohol (8). The alcohol (8) is oxidized with oxalyl chloride and DMSO to give 3-(1-Triphenylmethyl-5-imidazoyl)cyclopropylpropanal (9). The anion of sulphone (10) is prepared by the reaction of the sulphone with strong base, preferably n-BuLi, and this anion is reacted with aldehyde (9), preferably at -78°C. The diastereoisomeric mixture of beta hydroxy-sulphones (11) produced, is treated with excess Raney nickel (W-2) at room temperature to give a mixture of alcohols (12). The Trityl protecting group can be removed, as previously described, to provide 1-(1(H)-5-imidazoyl)-cyclopropyl alcohols (13).

D. PREPARATION OF COMPOUNDS WHEREIN A IS -CH=CH-(Trans Olefins)

Scheme IV

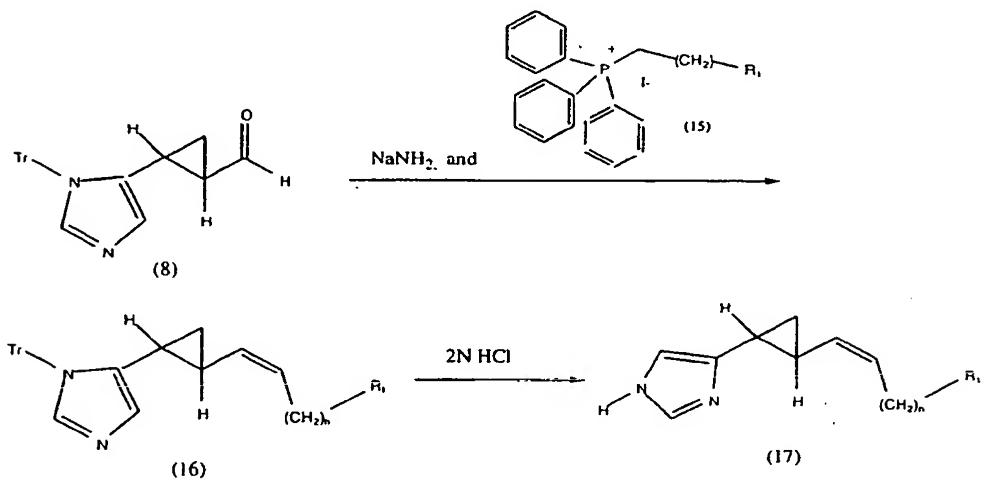


SCHEME IV

According to the foregoing reaction scheme IV, the diastereoisomeric mixture of beta hydroxy sulphones (10) synthesized as described in scheme III, is treated with excess 2 - 3% Na(Hg) in methanol in the presence of 4 equivalents of sodium hydrogen phosphate buffer to provide after separation of olefin isomers the 1-(1-Triphenylmethyl-5-imidazoyl)-cyclopropyl trans olefin (13). Subsequent trityl deprotection gives 1-(1H-5-imidazoyl)-cyclopropyl trans olefin (14).

E. PREPARATION OF COMPOUNDS WHEREIN A IS -CH=CH-(Cis Olefins)

Scheme V

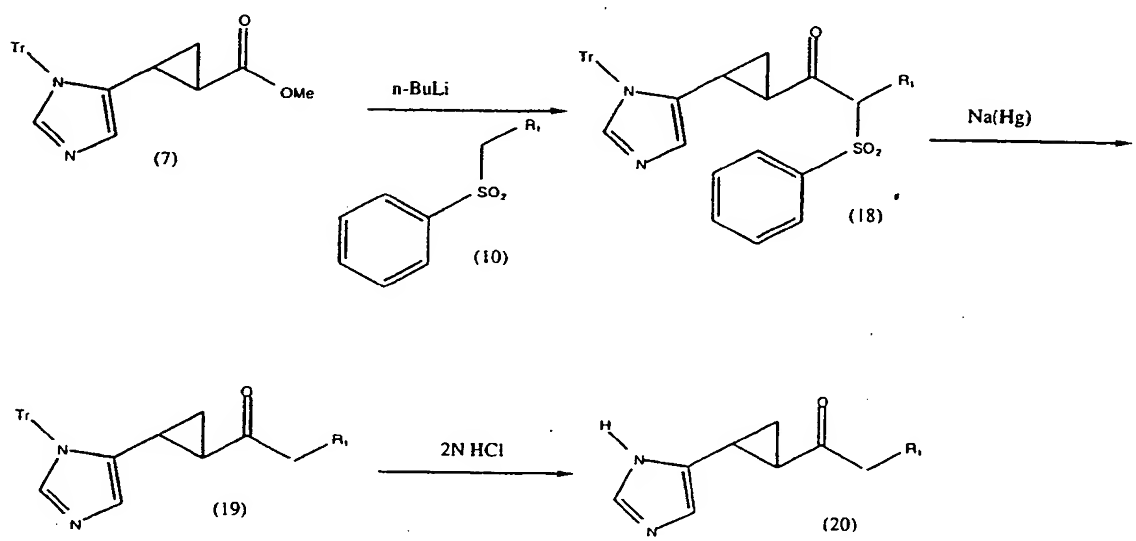


SCHEME V

According to the foregoing reaction scheme V, 3-(1-Triphenylmethyl-5-imidazoyl)cyclopropylpropanal (8) was converted to olefin (16) via treatment with the Wittig reagent derived from treatment of the phosphonium iodide salt (15) with strong base, preferably $NaNH_2$. As before, the Trityl protecting group was removed by treatment with aqueous 2N HCl to give 1-(1H-5-imidazoyl)cyclopropyl cis olefin (17).

F. PREPARATION OF COMPOUNDS WHEREIN A IS $-COCH_2-$

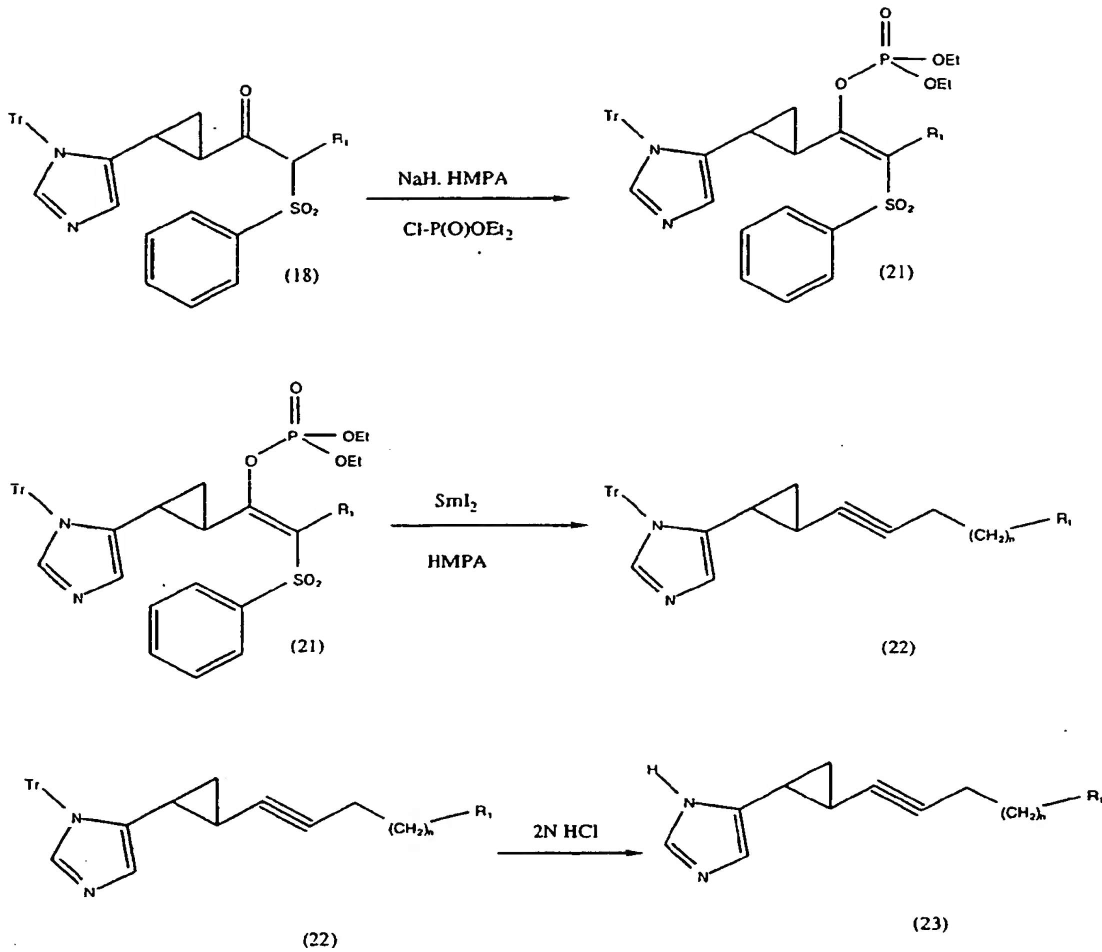
Scheme VI



SCHEME VI

According to the foregoing reaction scheme VI, 1-(1-Triphenylmethyl-5-imidazoyl)cyclopropylcarboxylic ester (7) is reacted with 2.5 equivalents of the sulfone anion derived from (10) at -78°C to give the keto-sulfone (18). Treatment with Al(Hg) or Na(Hg) provides - 1-(1-Triphenylmethyl-5-imidazoyl)cyclopropyl ketone (19). Trityl deprotection with 2N HCl gives 1-(1H-5-imidazoyl)cyclopropylketone (20).

Scheme VII

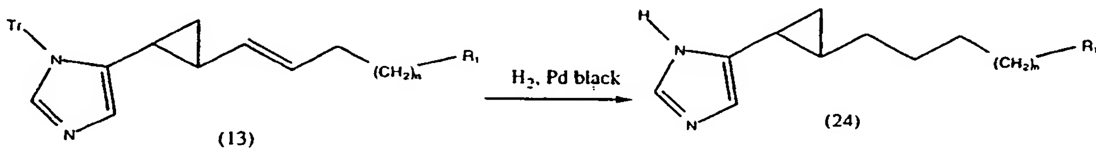


SCHEME VII

According to the foregoing reaction scheme VII, the 1-(1-Triphenylmethyl-5-imidazoyl)-cyclopropyl keto sulfone (18), prepared following scheme VI, is treated with NaH in the presence of HMPA, followed by diethyl phosphorochloridate to give the enol phosphate (21). Treatment of enol phosphate (21) with excess SmI_2 in THF/HMPA provides 1-(1-Triphenylmethyl-5-imidazoyl)cyclopropyl acetylenes (22). Finally, deprotection of the trityl protecting group with 2N HCl gives 1-(1H-5-imidazoyl)-cyclopropyl acetylenes (23).

H. PREPARATION OF COMPOUNDS WHEREIN A IS $-CH_2CH_2-$

Scheme VIII



(13)

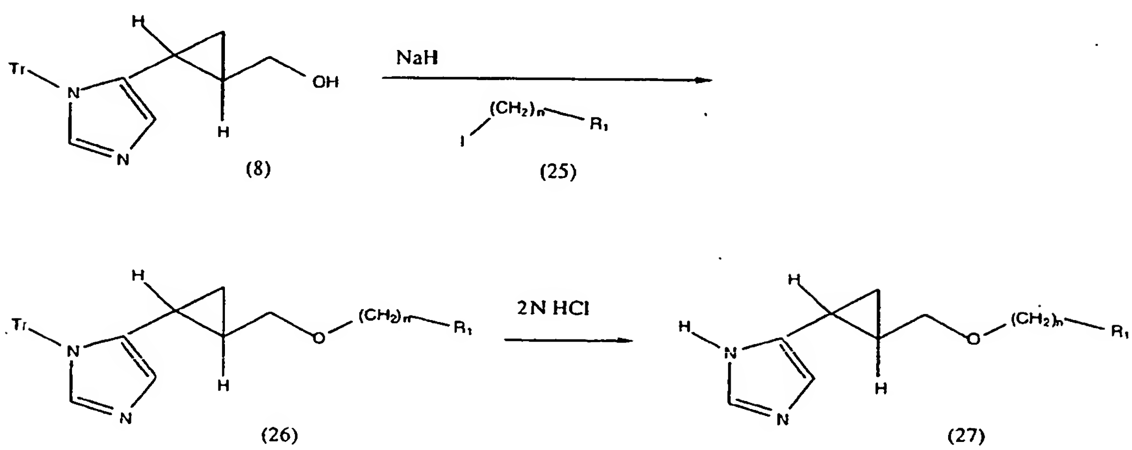
(24)

SCHEME VIII

According to the foregoing reaction scheme VIII, the 1-(1-Triphenylmethyl-5-imidazoyl)-cyclopropyl trans olefin (13), prepared following scheme IV, is subjected to catalytic hydrogenation under the conditions described by Zervas et al., *J. Am. Chem. Soc.*, 78: 1359 (1956), to reduce the carbon-carbon double bond and deprotect the trityl group, and provide the 1-(1H-5-imidazoyl)-cyclopropane (24).

I. PREPARATION OF COMPOUNDS WHEREIN A IS $-CH_2O-$

Scheme IX

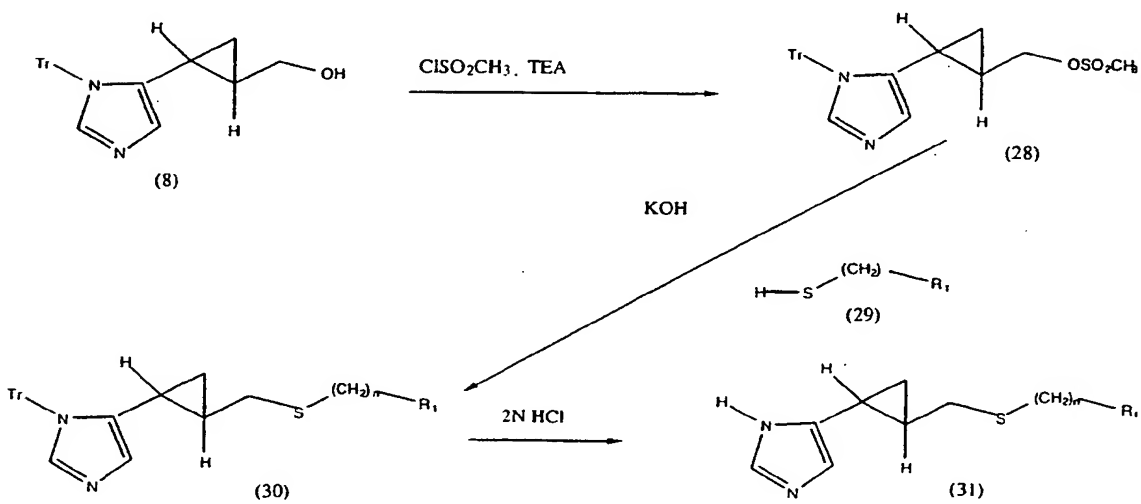


SCHEME IX

According to the foregoing reaction scheme IX, the racemic mixture of 1-(1-Triphenylmethyl-5-imidazoyl)-cyclopropyl alcohols (8), prepared following the procedure outlined in scheme III, is treated with sodium hydride and reacted with iodide (25) to provide 1-(1-Triphenylmethyl-5-imidazoyl)-cylcopropyl ethers (26). The trityl protecting group is removed with aqueous 2N HCl to give 1-(1H-5-imidazoyl) cyclopropyl ether (27).

J. PREPARATION OF COMPOUNDS WHEREIN A IS $-CH_2S-$

Scheme X

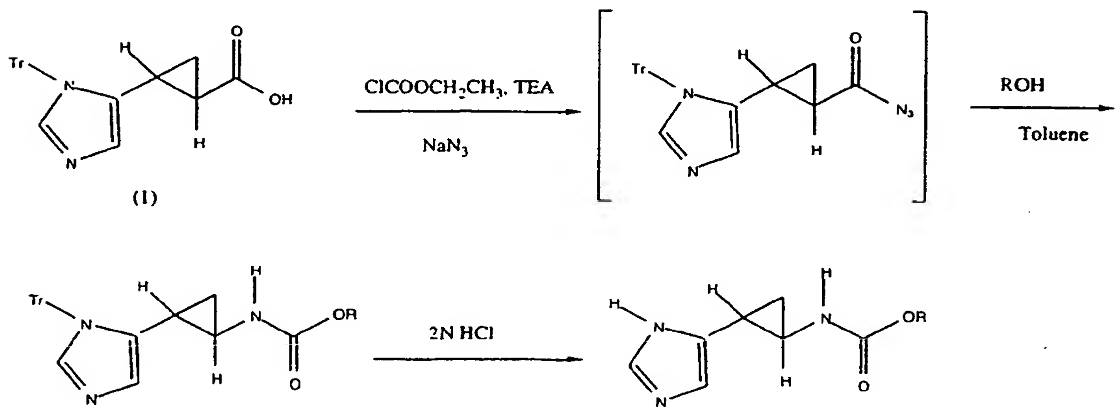


SCHEME X

According to the foregoing reaction scheme X, the racemic mixture of 1-(1-Triphenyl-5-imidazoyl)-cyclopropyl alcohols (8) is treated with methanesulfonyl chloride and triethylamine to provide the corresponding mesylates (28). The mesylates (28) were treated with thiolate (29) to afford 1-(1-Triphenyl-5-imidazoyl)-cyclopropyl sulfides (30). The trityl protecting group is removed with aqueous 2N HCl to give 1-(1H-5-imidazoyl) cyclopropyl sulfides (31).

K. PREPARATION OF COMPOUNDS WHEREIN A IS -NH-(COO)-R

Scheme XI



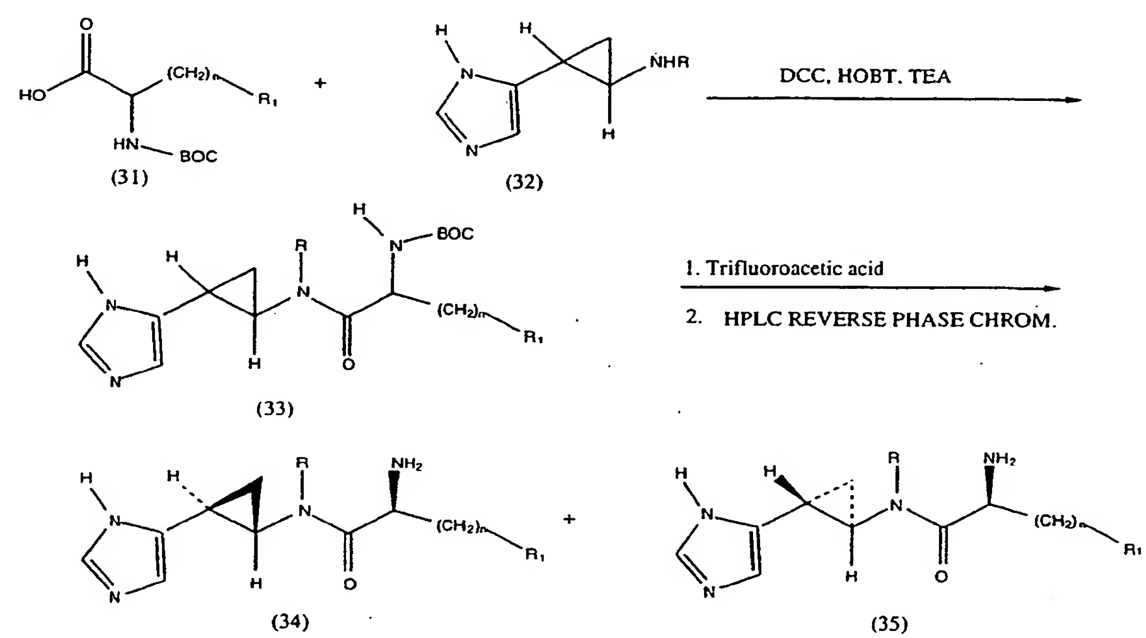
(1) (32) (33)

SCHEME XI

According to the foregoing reaction scheme XI, 3-(1-Triphenylmethyl-5-imidazoyl)cyclopropanecarboxylic acid (1) is converted to an activated ester through the action of ethyl chloroformate and triethylamine. The activated ester is reacted in situ with sodium azide to provide the acyl azide, which is heated at reflux in toluene in the presence of alcohol, to give 1-(1-Triphenylmethyl-5-imidazoyl)cyclopropyl carbamate (32). Deprotection of the trityl group with 2N HCl gives 1-(1H-5-imidazoyl)cyclopropyl carbamate (33).

L. PREPARATION OF COMPOUNDS WHEREIN A IS -NHCO- OR -N(CH_3)CO- AND X IS H or NH_2-

Scheme XII

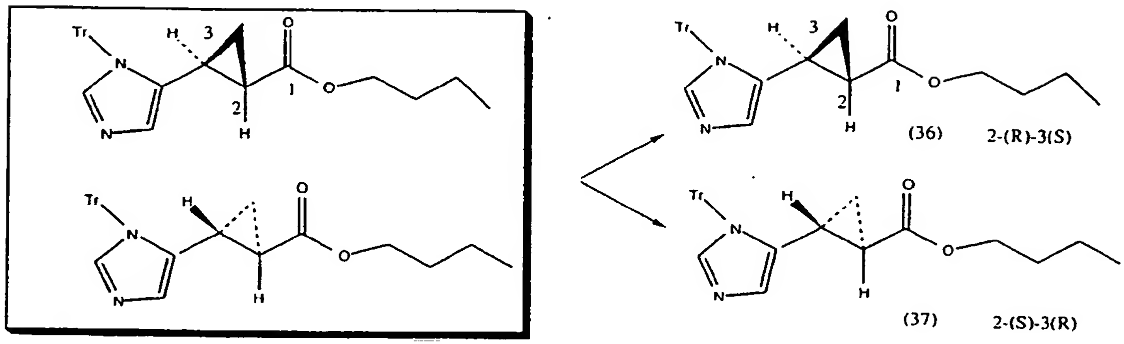


SCHEME XII

According to the foregoing reaction scheme XII, the racemic mixture of 2-(1H-5-imidazoyl)-2(R)-1(S)-cyclopropylamine (R=H) and 2-(1H-5-imidazoyl)-2(S)-1(R)-cyclopropylamine (32), prepared according to the method of Burger et al., *J. Med. Chem.*, (1970), 13: 33-35, is reacted with the appropriate amino acid (31), (natural L-configuration), under standard peptide coupling conditions using DCC and HOBT. After the reaction is complete (tlc or hplc analysis), the diastereomeric mixture of amides (33) is separated by reverse phase HPLC chromatography using CH_3CN/ H_2O / 0.1% TFA as eluent to provide pure diastereoisomers (34) and (35).

M. PREPARATION OF CHIRAL CYCLOPROPANE COMPOUNDS

Scheme XIII



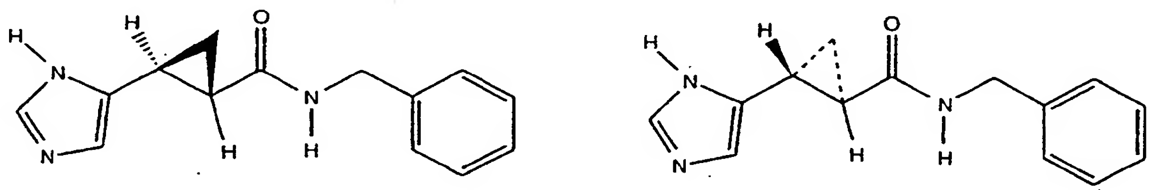
SCHEME XIII

Chiral cyclopropane containing compounds that are claimed as histamine H_3 receptor antagonists were prepared from 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-3(S)-cyclopropanoic butyl ester (36) or 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-3(R)-cyclopropanoic butyl ester (37). The racemic mixture of these enantiomers were separated using a chiral column (Regis serial # 0112201) and a mobile phase of 90/10 Hexane/Isopropyl alcohol. Using this column, enantiomer (37) had a retention time of 7.315 minutes, and enantiomer (36) had a retention time of 5.787 minutes.

The present invention is further illustrated by the following representative examples:

EXAMPLE 1

Preparation of racemic mixture of N-(1-Benzyl)-3-[(1H-imidazol-5-yl)]-2(R)-3(S)-cyclopropanamide and N-(1-Benzyl)-3-[(1H-imidazol-5-yl)]-2(S)-3(R)-cyclopropanamide hydrochloride



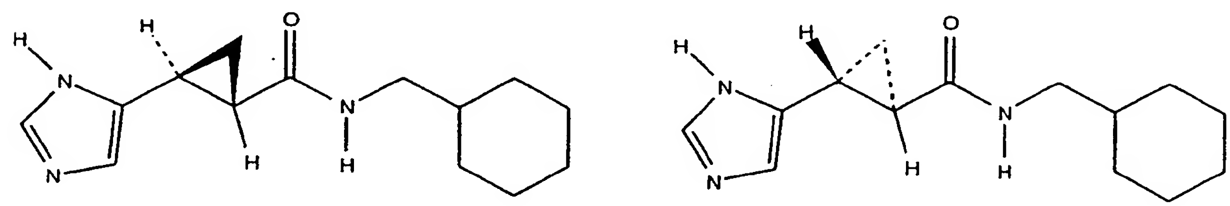
The racemic mixture of 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-3(S)-cyclopropanoic acid and 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-3(R)-cyclopropanoic acid, prepared according to the method of Burger, et al., *J. Med. Chem.*, (1970), 13: 33-35, (0.334 g, 0.84 mM) was suspended in 5 ml of distilled water. Sufficient acetone (35 ml) was added to complete solution, and the homogeneous solution was cooled to 0-5° C. Triethylamine (0.101 g, 1.0 mM) in 5 ml of acetone was added, followed by dropwise addition of ethyl chloroformate (0.108 g, 1.0 mM). The reaction mixture was stirred for 30 minutes at 0°C, and then a solution of benzylamine (0.16 g, 1.5 mM) in 10 ml of acetone was added dropwise. The reaction mixture was stirred at 0 - 5° C for 1 hour, and then added to cold saturated ammonium chloride solution (100 ml), and extracted with ethyl acetate (2X 100 ml). The combined ethyl acetate extracts were separated, dried over magnesium sulfate, filtered, and evaporated in vacuo to provide a crude yellow oil. The crude yellow oil was directly dissolved in 5 ml of methanol. 10 ml of 2N HCl was added, and the mixture heated at reflux for 40 minutes. The reaction mixture was cooled to room temperature, filtered, and the filtrate evaporated in vacuo to dryness. The remaining solid was triturated with a 1:1 mixture of ethyl acetate/hexanes (2X 30 ml), collected by filtration, and dried under vacuum to give 109 mgs of a racemic mixture of N-(1-Benzyl)-3-[(1H-imidazol-5-yl)]-2(R)-3(S)-cyclopropanamide and N-(1-Benzyl)-3-[(1H-imidazol-5-yl)]-2(S)-3(R)-cyclopropanamide hydrochloride (47%).

NMR (CD_3OD), 300 MHz): d 7.74 (s, 1H), 7.30 (m, 5H), 6.92 (s, 1H), 4.37 (AB q, 2H), 2.35 (m, 1H), 1.88 (m, 1H), 1.42 (m, 1H), 1.24 (m, 1H).

Mass Spectrum (DCI/NH_3): 242 $(M+1)^{+}$, MW= 241.2942, $C_{14}H_{15}N_3O_1$.

EXAMPLE 2

Preparation of racemic mixture of N-(1-cyclohexylmethyl)-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-(1-cyclohexylmethyl)-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride

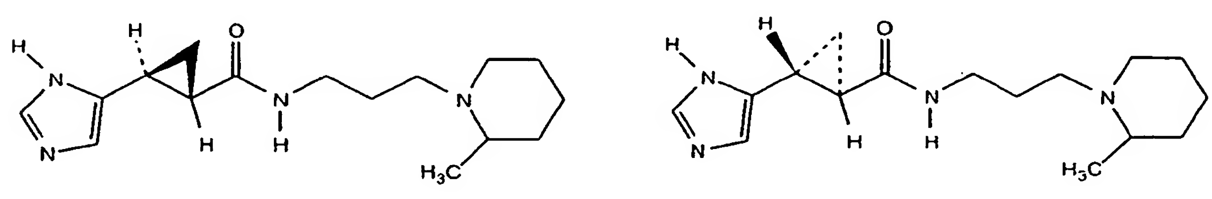


The racemic mixture of N-(1-cyclohexylmethyl)-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-(1-cyclohexylmethyl)-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except cyclohexanemethyl-amine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 7.78 (s, 1H), 6.92 (s, 1H), 3.02 (m, 2H), 2.30 (m, 1H), 1.84 (m, 1H), 1.74 (m, 4H), 1.45 (m, 1H), 1.35 (m, 1H), 1.22 (m, 3H), 0.94 (m, 2H). Mass Spectrum (DCI/NH_3): 248 $(M+1)^+$, MW= 247.3422, $C_{14}H_{21}N_3O_1$.

EXAMPLE 3

Preparation of racemic mixture of N-[1-(3-Aminopropyl)-2-pipecoline]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[1-(3-Aminopropyl)-2-pipecoline]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride



The racemic mixture of N-[1-(3-Aminopropyl)-2-pipecoline]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[1-(3-Aminopropyl)-2-pipecoline]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as

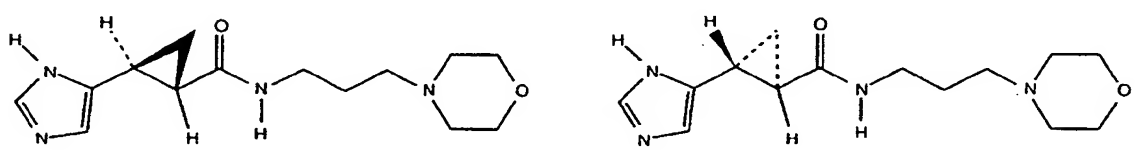
described in Example 1, except 1-(3-Aminopropyl)-2-pipecoline was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.80 (s, 1H), 7.38 (s, 1H), 3.55 (m, 1H), 3.3 (m, 3H), 3.1 (m, 3H), 2.44 (m, 1H), 1.96 (m, 4H), 1.8 (m, 2H), 1.55 (m, 2H), 1.39 (d, 3H, J=6Hz), 1.35 (m, 4H).

Mass Spectrum (DCI/NH_3): 291 $(M+1)^+$, MW= 290.4109, $C_{16}H_{26}N_4O_1$.

EXAMPLE 4

Preparation of racemic mixture of N-[4-(3-Aminopropyl)morpholine]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[4-(3-Aminopropyl) morpholine]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride



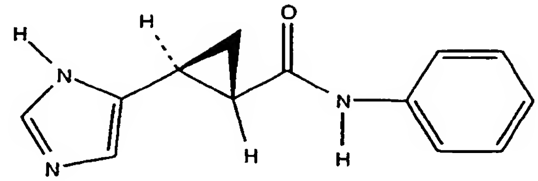
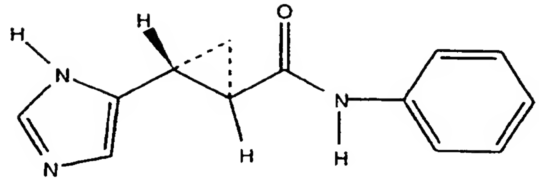
The racemic mixture of N-[4-(3-Aminopropyl)morpholine]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[4-(3-Aminopropyl)morpholine]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except 4-(3-Aminopropyl)morpholine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.80 (s, 1H), 7.38 (s, 1H), 4.05 (m, 2H), 3.80 (m, 2H), 3.50 (m, 2H), 3.32 (m, 3H), 3.16 (m, 4H), 2.44 (m, 1H), 2.00 (m, 3H), 1.54 (m, 1H), 1.35 (m, 1H).

Mass Spectrum (DCI/NH_3): 279 $(M+1)^+$, MW= 278.3422, $C_{14}H_{22}N_4O_1$.

EXAMPLE 5

Preparation of racemic mixture of N-(phenyl)-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-(phenyl)-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride.

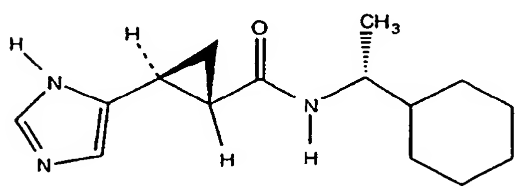
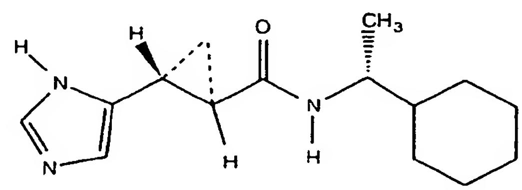



The racemic mixture of N-(phenyl)-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-(phenyl)-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except aniline was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 7.56 (s, 1H), 7.53 (dd, 2H), 7.28 (m, 2H), 7.06 (m, 1H), 6.91 (s, 1H), 2.42 (m, 1H), 2.02 (m,1H), 1.48 (m, 1H), 1.33 (m, 1H).
Mass Spectrum (DCI/NH_3): 228 $(M+1)^+$, MW= 227.2672, $C_{13}H_{13}N_3O_1$.

EXAMPLE 6

Preparation of racemic mixture of N-[(R)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[(R)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride

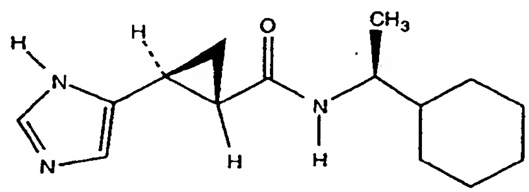



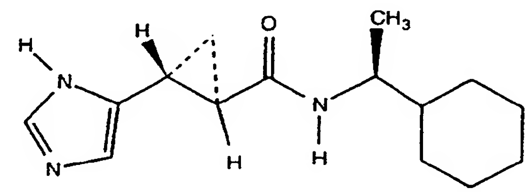
The racemic mixture of N-[(R)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[(R)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except (R)-1-Cyclohexylethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.78 (s, 1H), 7.36 (s, 1H), 3.73 (m, 1H), 2.41 (m, 1H), 1.97 (m,1H), 1.74 (m, 6H), 1.50 (m, 2H), 1.40-0.91 (m, 5H), 1.09 (d, 3H).
Mass Spectrum (DCI/NH_3); 262 $(M+1)^+$ MW=261.343; $C_{15}H_{23}N_3O_1$.

EXAMPLE 7

Preparation of racemic mixture of N-[(S)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[(S)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride



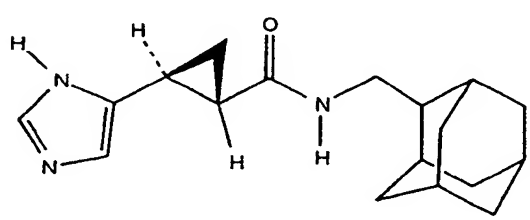


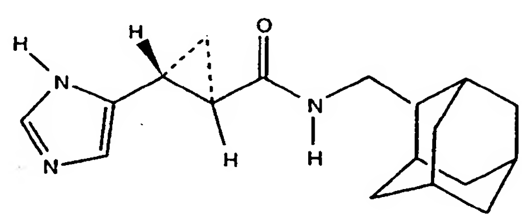
The racemic mixture of N-[(S)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[(S)-1-Cyclohexylethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except (S)-1-Cyclohexylethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.78 (s, 1H), 7.36 (s, 1H), 3.73 (m, 1H), 2.41 (m, 1H), 1.97 (m,1H), 1.74 (m, 6H), 1.50 (m, 2H), 1.40-0.91 (m, 5H), 1.09 (d, 3H).
Mass Spectrum (DCI/NH_3): 262 $(M+1)^+$ MW=261.343, $C_{15}H_{23}N_3O_1$.

EXAMPLE 8

Preparation of racemic mixture of N-[1-Adamantylmethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride and N-[1-Adamantylmethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide.





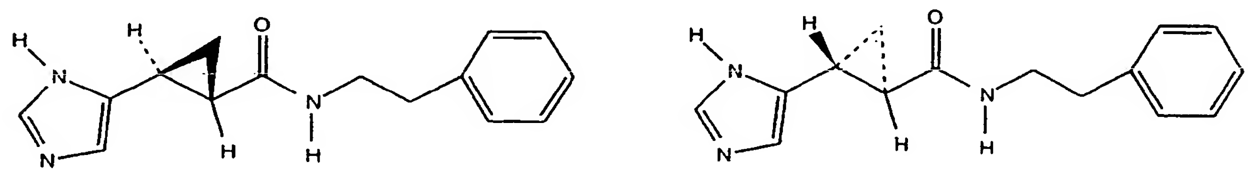
The racemic mixture of N-[1-Adamantylmethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[1-Adamantylmethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except 1-Adamantylmethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.58 (s, 1H), 6.84 (s, 1H), 3.36 (m, 1H), 2.31 (m, 1H), 2.08-1.06 (m, 14H).

Mass Spectrum (DCI/NH_3): 300 $(M+1)^+$ MW= 299.4181, $C_{18}H_{25}N_3O_1$.

EXAMPLE 9

Preparation of racemic mixture of N-[2-Phenylethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[2-Phenylethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride.



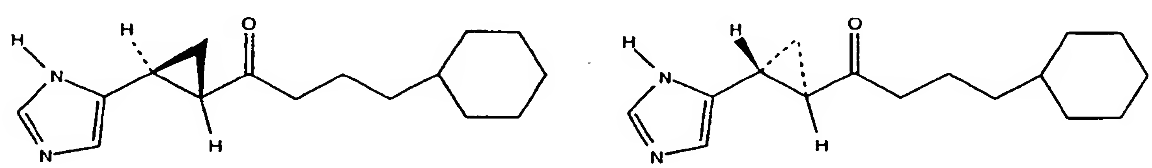
The racemic mixture of racemic mixture of N-[2-Phenylethyl]-3-(1H-imidazol-5-yl)-2(R)-3(S)-cyclopropanamide and N-[2-Phenylethyl]-3-(1H-imidazol-5-yl)-2(S)-3(R)-cyclopropanamide hydrochloride was prepared as described in Example 1, except 2-Phenylethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.78 (s, 1H), 7.32 (s, 1H), 7.22 (m, 5H), 3.44 (t, 2H), 2.8 (t, 2H), 2.40 (m, 1H), 1.95 (m, 1H), 1.50 (m, 1H), 1.31 (m, 1H).

Mass spectrum (DCI/NH_3): 256 $(M+1)^+$ MW= 255.3211, $C_{15}H_{17}N_3O_1$.

EXAMPLE 10

Preparation of racemic mixture of 3-(1-H-imidazol-5-yl)-2(S)-3(R)-cyclopropyl-3'-cyclohexylpropanone and 3-(1-H-imidazol-5-yl)-2(R)-3(S)-cyclopropyl-3'-cyclohexylpropanone.



Step 1.

Racemic mixture of 3-(1-Triphenylmethyl-5-imidazoyl)-2(S)-3(R)-cyclopropyl-3'-cyclohexylpropanone and 3-(1-H-imidazol-5-yl)-2(R)-3(S)-cyclopropyl-3'-cyclohexylpropanone.

To a 100 ml flask, placed under N_2, and charged with magnesium metal (0.076 g, 3.12 mM) and 3 ml of anhydrous ether, was added dropwise (25 min), an ether solution (15 ml) of 3-cyclohexyl-propyl iodide (0.756 g, 3.0 mM). After 3 hours at room temperature the racemate of N,O-(Dimethyl)-3-(1-Triphenylmethyl-5-imidazoyl)-2(R)-3(S)-cyclopropanamide and N,O-(Dimethyl)-3-(1-Triphenylmethyl-5-imidazoyl)-2(S)-3(R)-cyclopropanamide (1.22 g, 2.8 mM) in 15 ml of anhydrous THF was added dropwise to the Grignard solution at 0° C. After 1 hour at 0° C, the reaction was warmed to 50°C, and kept at that temperature for 15 hours. The reaction mixture was cooled, and quenched by the addition of saturated ammonium chloride (100 ml), and extracted (2X 100 ml) with ethyl acetate. The ethyl acetate extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo to give a crude yellow oil. The crude oil was purified using silica gel column chromatography (ethyl acetate: hexanes, 1:1) to provide 250 mgs of a racemic mixture of 3-(1-Triphenylmethyl-5-imidazoyl)-2(S)-3(R)-cyclopropyl-3'-cyclohexylpropanone and 3-(1-Triphenylmethyl-5-imidazoyl)-2(R)-3(S)-cyclopropyl-3'-cyclohexylpropanone (18%).

NMR ($CDCl_3$, 300 MHz): d 7.3 (m, 12H), 7.10 (m, 4H), 6.72 (d, 1H), 2.38 (m, 3H), 1.8-1.6 (m, 2H), 1.5 (m, 9H), 1.20 (m, 7H).

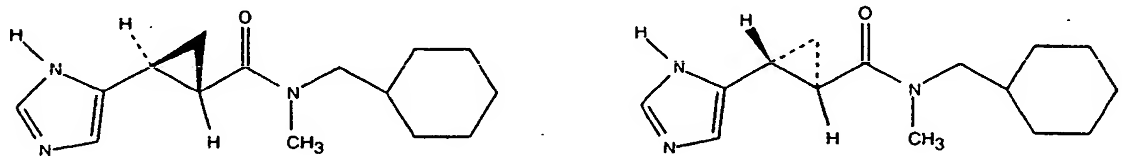
Step 2.

The racemic mixture of 3-(1-Triphenylmethyl-5-imidazoyl)-2(S)-3(R)-cyclopropyl-3'-cyclohexylpropanone and 3-(1-Triphenylmethyl-5-imidazoyl)-2(R)-3(S)-cyclopropyl-3'-cyclohexylpropanone (0.250 g, 0.5 mM) was heated at reflux in 10 ml of 2N HCl and 2 ml of methanol for 40 minutes. The reaction mixture was cooled, filtered, and then neutralized to pH 7 with 5% sodium hydroxide solution, and extracted with chloroform (2X 50 ml). The chloroform extracts were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo to give a crude yellow oil. The crude oil was purified using preparative tlc with ($CHCl_3$: MeOH, 80:20) to afford 75 mgs of a racemic mixture of 3-(1-H-imidazol-5-yl)-2(S)-3(R)-cyclopropyl-3'-cyclohexylpropanone and 3-(1-H-imidazol-5-yl)-2(R)-3(S)-cyclopropyl-3'-cyclohexylpropanone (58%).

NMR (CD_3OD, 300 MHz): d 8.8 (d, 1H), 7.37(m, 1H), 2.47 (m, 2H), 2.14 (dt, 2H), 1.69 (m, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.32-1.10 (m, 13H), 0.87 (m, 2H).
Mass Spectrum (DCI/NH_3); 261 $(M+1)^+$ MW=260.3814; $C_{16}H_{24}N_2O_1$.

EXAMPLE 11

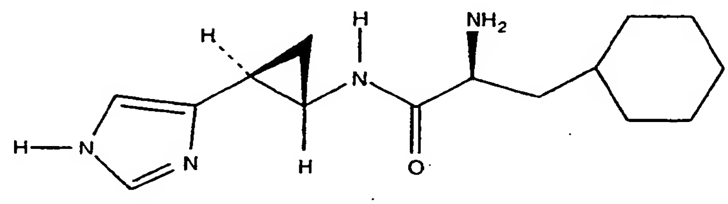
Preparation of racemic mixture of N,N-(1-Methyl, 1-Cyclohexanemethyl)-3-[(1H-imidazol-5-yl)]-2(R)-3(S)-cyclopropanamide and N,N-(1-Methyl, 1-Cyclohexanemethyl)-3-[(1H-imidazol-5-yl)]-2(S)-3(R)-cyclopropanamide.



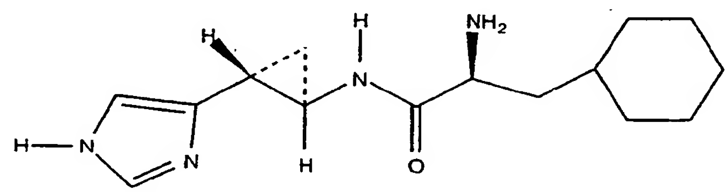
N,N-(1-Methyl,1-Cyclohexanemethyl)-3-[(1H-imidazol-5-yl)]-2(R)-3(S)-cyclopropanamide and N,N-(1-Methyl, 1-Cyclohexanemethyl)-3-[(1H-imidazol-5-yl)]-2(S)-3(R)-cyclopropanamide was prepared as described in Example 1 except, N,N-(1-Methyl, 1-Cyclohexanemethyl)amine was used instead of benzylamine. The intermediate, N,N-(1-Methyl, 1-Cyclohexanemethyl)-3-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-3(S)-cyclopropanamide and N,N-(1-Methyl,1-Cyclohexanemethyl)-3-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-3(R)-cyclopropanamide was purified by silica gel column chromatography using (ethyl acetate:hexanes,4:6). The free base of N,N-(1-Methyl,1-Cyclohexanemethyl)-3-[(1H-imidazol-5-yl)]-2(R)-3(S)-cyclopropanamide and N,N-(1-Methyl, 1-Cyclohexanemethyl)-3-[(1H-imidazol-5-yl)]-2(S)-3(R)-cyclopropanamide hydrochloride generated in the trityl deprotection step was made by neutralizing with 5% sodium hydroxide, extracting into $CHCl_3$, drying over magnesium sulfate, filtration, and evaporation in vacuo to provide a white foam.

NMR (CD_3OD, 300 MHz): d 7.78 (s, 1H), 6.92 (s, 1H), 3.02 (m, 2H), 2.30 (m, 1H), 2.20 (s, 3H),1.84 (m, 1H), 1.74 (m, 4H), 1.45 (m, 1H), 1.35 (m, 1H), 1.22 (m, 3H), 0.94 (m, 2H).
Mass Spectrum (DCI/NH_3): 262 $(M+1)^+$, MW= 261.3692, $C_{15}H_{23}N_3O_1$.

EXAMPLE 12 and 13

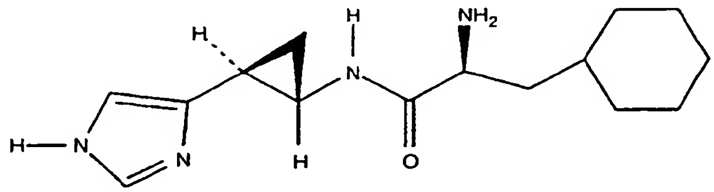


and



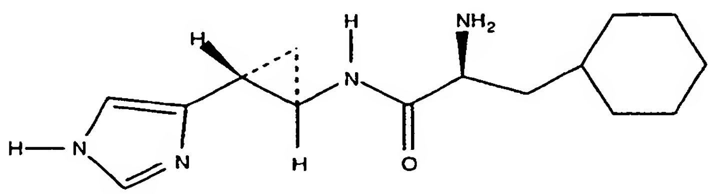
Preparation of the L-Cyclohexylalanine amide of 3(S)-(1H-5-imidazoyl)-2(R)-cyclopropylamine and the the L-Cyclohexylalanine amide of 3(R)-(1H-5-imidazoyl)-2(S)-cyclopropylamine Boc-Cyclohexylalanine -Dicyclohexylamine salt (0.497g, 1.1mM) was added to a mixture of ethyl acetate (25 ml) and 0.5 N HCl (25ml) for 30 minutes. The ethyl acetate layer was separated, washed with water (3X 100 ml), dried over $MgSO_4$, and evaporated to give the Boc-Cyclohexylalanine free acid (1.1mM). The acid was dissolved in 25 ml of THF and cooled to 5°C under N_2. The acid was converted into a mixed anhydride by treatment with N-methyl morpholine (110ul, 1mM) and Isobutylchloroformate (130 ul, 1 mM). After stirring for 20 minutes, a solution of a racemic mixture of 2-(R)-3(S)-(1H-5-imidazoyl)-cyclopropylamine and 2-(S)-3(R)-(1H-5-imidazoyl)-cyclopropylamine (200 mgs, 1 mM) and triethylamine (284 ul, 2 mM) in 2 ml of water was added. After 2 hours, the reaction mixture was partioned between ethyl acetate (50 ml) and water (50 ml), the ethyl acetate layer was washed with saturated sodium bicarbonate solution, water, then dried over sodium sulfate, filtered, and evaporated in vacuo to give the BOC protected amine of L-Cyclohexylalanine amide of 3(S)-(1H-5-imidazoyl)-2(R)-cyclopropylamine and its diastereisomer the L-Cyclohexylalanine amide of 3(R)-(1H-5-imidazoyl)-2(S)-cyclopropylamine. The BOC group was deprotected by treating the crude amides directly with Trifluoroacetic acid (5 ml) for 30 minutes at r.t. The TFA was evaporated, and the residue triturated with ether to provide the di-trifluoroacetic acid salt of the diastereisomeric mixture of L-Cyclohexylalanine amide of 3(S)-(1H-5-imidazoyl)-2(R)-cyclopropylamine and the

L-Cyclohexylalanine amide of 3(R)-(1H-5-imidazoyl)-2(S)-cyclopropylamine (300 mgs). The diastereoisomers were separated using reverse phase HPLC.



Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.44 (s, 1H), 7.18 (s, 1H), 3.88 (m, 1H), 2.87 (m, 1H), 2.09 (m, 1H), 1.6 (m, 6H), 1.27 (m, 2H), 1.1 (m, 5H), 0.88 (m, 2H).
Mass Spectrum (+FAB): [277 $(M+1)^+$, 100%] MW= 276.3839, $C_{15}H_{24}N_4O_1$.
Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1n, 0%, 25 ms, 25%, 30 ms, 100%; rt. 20.07 min.



Di-Trifluoroacetic acid salt

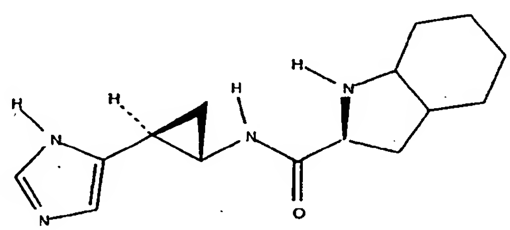
NMR (D_2O, 300 MHz): d 8.44 (s, 1H), 7.18 (s, 1H), 3.88 (m, 1H), 2.87 (m, 1H), 2.06 (m, 1H), 1.6 (m, 6H), 1.27 (m, 2H), 1.1 (m, 5H), 0.88 (m, 2H).
Mass Spectrum (+FAB): [277 $(M+1)^+$, 100%] MW= 276.3839, $C_{15}H_{24}N_4O_1$.
Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1n, 0%, 25 ms, 25%, 30 ms, 100%; rt. 18.773 min.

EXAMPLES 14 AND 15

Preparation of the L-Octahydro-indolyl-2-carboxylic amide of 3(S)-(1H-5-imidazoyl)-2(R)-cyclopropylamine and the the L-Octahydro-indolyl-2-carboxylic amide of 3(R)-(1H-5-imidazoyl)-2(S)-cyclopropylamine.

The preparation of the L-Octahydro-indolyl-2-carboxylic amide of 3(S)-(1H-5-imidazoyl)-2(R)-cyclopropylamine and the the L-Octahydro-indolyl-2-carboxylic amide of 3(R)-(1H-5-imidazoyl)-2(S)-cyclopropylamine were prepared in the same way as examples 12 and 13 except L-Octahydro-indolyl-2-carboxylic acid was used instead of L-Cyclohexylalanine.

EXAMPLE 14



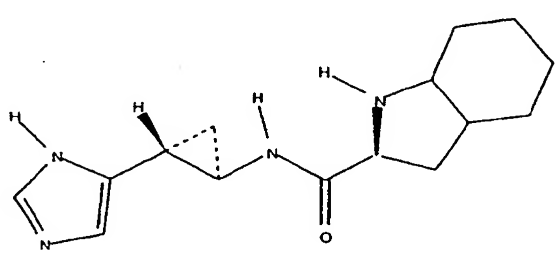
Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.4 (s, 1H), 7.06 (s, 1H), 4.25 (m, 1H), 3.65 (m, 1H), 2.8 (m, 1H), 2.30 (m, 2H), 2.2-0.90 (m, 12H).

Mass Spectrum (+FAB): [275 $(M+1)^+$, 100%] MW= 274.3678, $C_{15}H_{22}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 0%, 20 ms, 20%, 25 ms, 100%, 30 ms, 0%; rt. 14.54 min.

EXAMPLE 15



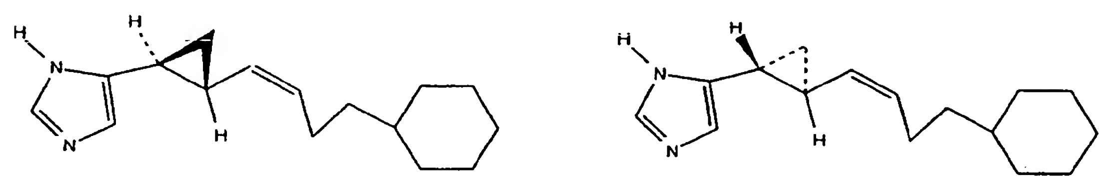
Di-Trifluoroacetic acid salt

NMR (D_2O, 300 MHz): d 8.4 (s, 1H), 7.06 (s, 1H), 4.25 (m, 1H), 3.65 (m, 1H), 2.8 (m, 1H), 2.30 (m, 2H), 2.1-1.0 (m, 12H).

Mass Spectrum (+FAB): [275 $(M+1)^+$, 100%] MW= 274.3678, $C_{15}H_{22}N_4O_1$.

Analytical HPLC: CH_3CN/H_2O/0.1% TFA; Gradient: 1nn, 0%, 20 ms, 20%, 25 ms, 100%, 30 ms, 0%; rt. 16.03 min.

EXAMPLE 16



Step 1

Preparation of racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-cis-3-hexene and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-cis-3-hexene.

3-cyclohexylpropyl triphenylphosphonium iodide (1.36 g, 2.64 mM) was suspended in 100 ml of dry THF at r.t. under N_2. Sodium amide (0.102 g, 2.64 mM) was added, and the red-orange solution stirred for 1 hour at r.t. The solution containing the ylide derived from 3-cyclohexylpropyl triphenylphosphonium iodide was cooled to -78°C, and a THF solution (35 ml) of a racemic mixture of 3 (R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropylcarboxaldehyde and 3 (S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropylcarboxaldehyde (1.0 g, 2.64 mM) was added slowly dropwise in 1 hour. After the addition of aldehyde was complete, the reaction was allowed to warm slowly to r.t. over a period of 5 hours. The reaction was quenched with saturated solution of ammonium chloride, and extracted with 2X 150 ml of ethyl acetate. The ethyl acetate layer was separated, dried with magnesium sulfate, and evaporated in vacuo to afford the crude olefin. Purification using silica gel chromatography gave 327 mgs of racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-cis-3-hexene and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-cis-3-hexene.

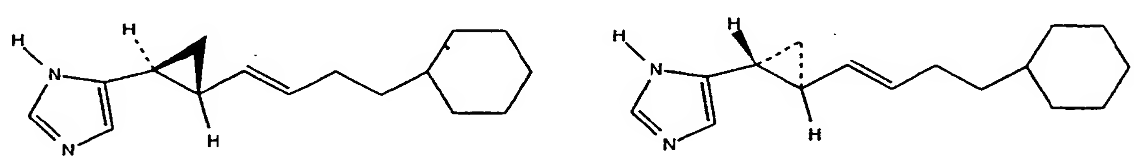
NMR ($CDCl_3$, 300 MHz): d 7.34-7.08 (m, 15H), 6.96 (d, 1H), 6.55 (d, 1H), 5.30 (m, 1H),4.84 (m, 1H), 2.14 (m, 1H), 2.00 (m, 1H), 1.93 (m, 1H), 1.78-0.76 (18H).
Mass Spectrum (DCI/NH_3): [488 $(M+1)^+$] MW= 486.7024, $C_{35}H_{38}N_2$.

Step 2

The racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-cis-3-hexene and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-cis-3-hexene (0.320 g, 0.657 mM) was dissolved in 10 ml of 90% acetic acid/10% water. The reaction mixture was heated at 60°C for 2 hours. The reaction mixture was cooled, added to 50 ml of 10% sodium hydroxide solution, and extracted with chloroform (2X 50 ml). The chloroform extracts were combined, dried over $MgSO_4$, and evaporated in vacuo. Purification by silica gel chromatography gave 103 mgs (viscous yellow glass) of a racemic mixture of 1(R)-[(1H-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-cis-3-hexene and 1(S)-[(1H-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-cis-3-hexene.

NMR (CD_3OD, 300 MHz): d 7.6 (s, 1H), 6.82 (s, 1H), 5.34 (m, 1H), 4.90 (m,1H), 2.18 (m, 2H), 1.90 (m, 3H), 1.60 (5H), 1.4-0.7 (m, 9H).
Mass Spectrum (DCI/NH_3): [245 $(M+1)^+$, 100%] MW= 244.3814, $C_{16}H_{24}N_2$.

EXAMPLE 17



Preparation of racemic mixture of 1(R)-[(1H-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-trans-3-hexene and 1(S)-[(1H-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-trans-3-hexene.

Step 1

3-cyclohexylpropyl phenyl sulphone (1.1 g, 4.13 mM) was dissolved in 40 ml of dry THF and cooled to -78°C under N_2. n-BuLi (1.65 ml, 4.13 mM) was added dropwise, and the solution stirred for 1 hour at -78°C. A THF solution (40 ml) of a racemic mixture of

3 (R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropylcarboxaldehyde and 3 (S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropylcarbox-aldehyde (1.56 g, 4.13 mM) was added dropwise in 15 minutes. After the addition of aldehyde was complete, the reaction was allowed to stirfor 30 minutes, and then quenched with saturated ammonium chloride solution (200 ml). The reaction mixture was extracted with 2X 150 ml of ethyl acetate. The ethyl acetate layer was separated, dried with magnesium sulfate, and evaporated in vacuo to afford the crude olefin. Purification using silica gel chromatography gave 1.01 g of racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-3-hydroxy-4-phenylsulphone-6-cyclohexyl-hexane and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-3-hydroxy-4-phenylsulphone-6-cyclohexyl-hexane.

NMR ($CDCl_3$, 300 MHz): d 7.92-7.5 (m, 5H), 7.34- 7.04 (m, 15H), 6.6-6.46 (4 doublets, 2H),3.76 (m, 0.5H), 3.67 (m,0.5H), 3.14 (m, 0.5H), 3.02 (m, 0.5H), 2.2-0.6 (m, 19H).

Step 2

The racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-3-hydroxy-4-phenylsulphone-6-cyclohexyl-hexane and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-3-hydroxy-4-phenylsulphone-6-cyclohexyl-hexane (0.260 g, 0.40 mM) was dissolved in 20 ml of dry dichloromethane at r.t. under N_2. Triethylamine (0.116 ml, 0.80 mM) was added, followed by Acetic anhydride (0.047 ml). The reaction was stirred for 5 days at r.t., water was added, and the dichloromethane layer separated, dried with magnesium sulfate, filtered, and evaporated in vacuo. Purification using silica gel column chromatography and eluting with ethyl acetate/hexanes (3:7) gave 260 mgs of (white foam) racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-3-acetoxy-4-phenylsulphone-6-cyclohexyl-hexane and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-3-acetoxy-4-phenylsulphone-6-cyclohexyl-hexane.

NMR ($CDCl_3$, 300 MHz): d 7.92-7.5 (m, 5H), 7.34- 7.04 (m, 15H), 6.6-6.46 (4 doublets, 2H),5.17 (m,0.5H), 5.04 (m, 0.5H), 3.76 (m, 0.5H), 3.02 (m, 0.5H), 2.2-0.6 (m, 19H), 2.1(s, 3H)CHN: $C_{43}H_{46}N_2S_1O_4$, MW= 686.9144, Calc: C: 75.19, H: 6.75, N: 4.07; Found: C: 74.79, H: 6.89, N: 4.10

Step 3

The racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-3-acetoxy-4-phenylsulphone-6-cyclohexyl-hexane and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-3-acetoxy-4-phenylsulphone-6-cyclohexyl-hexane (0.103 g, 0.15 mM) was dissolved in 8 ml of dry methanol at 0^0C under N_2. Na_2HPO_4 (0.084 g, 0.60 mM) was added, followed by 3 g of 2% Na(Hg). The reaction mixture was stirred at 0-5°C for 2 hours, and then filtered through a pad of celite. The filtrate was evaporated, and the residue partioned between $CHCl_3$ and water. The $CHCl_3$ layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification using tlc afforded 52 mgs of (viscous yellow glass) racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-trans-3-hexene and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-trans-3-hexene.

NMR ($CDCl_3$, 300 MHz): d 7.34-7.08 (m, 15H), 6.50 (d, 1H), 6.53 (d, 1H), 5.50 (m, 0.5H),5.30 (m, 0.5H),5.06 (m, 0.5H), 4.84 (m, 0.5H), 2.14 (m, 1H), 2.00 (m, 1H), 1.93 (m, 1H), 1.78-0.76 (18H).

Step 4

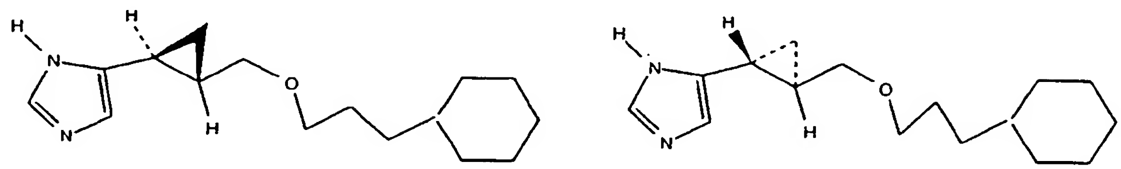
The racemic mixture of 1(R)-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-trans-3-hexene and 1(S)-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-trans-3-hexene (0.052 g,0.106mM) was heated at 80^0C in 1N HCl (6 ml) and ethanol (2 ml) for 30 minutes. The volatiles were removed by rotary evaporation, and the residue partioned between $CHCl_3$ (20 ml) and 10% NaOH solution. The $CHCl_3$ layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification using tlc gave 17 mgs of a racemic mixture of 1(R)-[(1H-5-imidazoyl)]-2(S)-cyclopropyl-6-cyclohexyl-trans-3-hexene and 1(S)-[(1H-5-imidazoyl)]-2(R)-cyclopropyl-6-cyclohexyl-trans-3-hexene.

NMR ($CDCl_3$, 300 MHz): d 7.34-7.08 (m, 15H), 6.50 (d, 1H), 6.53 (d, 1H), 5.50 (m, 0.5H),5.30 (m, 0.5H), 5.06 (m, 0.5H), 4.84 (m, 0.5H), 2.14 (m, 1H), 2.00 (m, 1H), 1.93 (m, 1H), 1.78-0.76 (18H).

Mass Spectrum (DCI/NH_3): [245 $(M+1)^+$, 100%] MW= 244.3814, $C_{16}H_{24}N_2$.

EXAMPLE 18

Preparation of racemic 3(S)-(1H-5-Imidazoyl)-2(R)-cyclopropyl-3'-cyclohexylpropyl ether and3(R)-(1H-5-Imidazoyl)-2(S)-cyclopropyl-3'-cyclohexylpropyl ether.

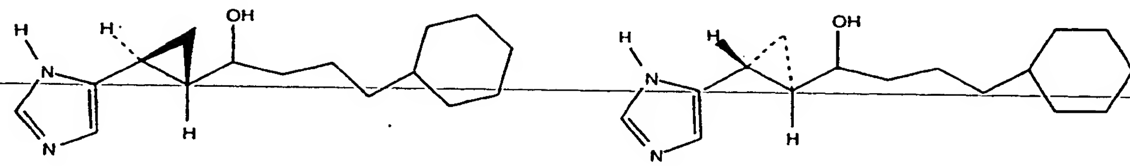


To a suspension of NaH (0.024 g, 1 mM) in 3 ml of dry DMF at 0°C under N_2 was added a racemic mixture of 3(R)-(1-Triphenylmethy-5-imidazoyl)-2(S)-cyclopropanol and 3(S)-(1-Triphenylmethy-5-imidazoyl)-2(R)-cyclopropanol (0.190 g, 0.5 mM). After stirring for 30 minutes, 3-cyclohexylpropyl iodide (0.372 g, 1.5 mM) in 1 ml of DMF was added, and the reaction stirred at 0°C for 20 minutes. The reaction was quenched with water (20 ml), and extracted with ethyl acetate (2X 30 ml). The ethyl acetate layer was washed with brine, separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford 3-(R)-(1-Triphenymethyl-5-imidazoyl)-2(S)-cyclopropyl-3'-cyclohexylpropyl ether and 3-(S)-(1-Triphenymethyl-5-imidazoyl)-2(R)-cyclopropyl-3'-cyclohexylpropyl ether. The trityl group was deprotected directly by treatment with 2N HCl (10 ml) and heating at 80°C for 30 minutes. The reaction mixture was cooled, filtered, and the filtrate evaporated in vacuo and triturated with ether to give 50 mgs of a racemic mixture of 3(S)-(1H-5-Imidazoyl)-2(R)-cyclopropyl-3'-cyclohexylpropyl ether and 3(R)-(1H-5-Imidazoyl)-2(S)-cyclopropyl-3'-cyclohexylpropyl ether.

NMR ($CDCl_3$, 300 MHz): d: 8.00 (d,1H), 7.26 (d,1H), 3.60(m,3H), 1.72 (m,1H), 1.48 (m, 1H),1.58 (m, 11H), 1.24 (4H), 0.96 (m,1H), 0.75 (m, 1H).
Mass Spectrum: (DCI/NH_3)[M+1, 263, 100%)] MW= 262.3974 : $C_{16}H_{26}O_1N_2$

EXAMPLE 19

Preparation of racemic 1(S)-(1H-5-Imidazoyl)-2(R)-cyclopropyl-3-hydroxy-6-cyclohexyl-hexane and 1(R)-(1H-5-Imidazoyl)-2(S)-cyclopropyl-3-hydroxy-6-cyclohexyl-hexane.

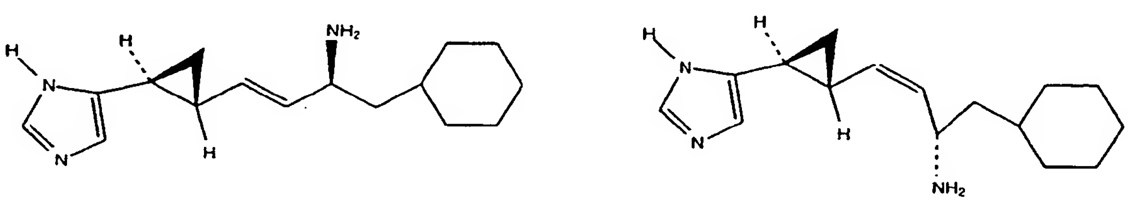


To a solution of a racemic mixture of 3-(1-Triphenylmethyl-5-imidazoyl)-2(S)-3(R)-cyclopropyl-3'-cyclohexylpropanone and 3-(1-Triphenylmethyl-5-imidazoyl)-2(R)-3(S)-cyclopropyl-3'-cyclohexylpropanone (251 mg, 0.5 mM) in 15 of methanol cooled to -20°C was added portionwise $NaBH_4$ (185 mgs, 5 mM) in ten minutes. After 10 minutes, the reaction was quenched with $KHSO_4$ solution (5 ml). The reaction mixture was partioned between ethyl acetate and water (50/50). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give crude alcohols. The alcohols were added to 10 ml of 2N HCl and heated at 80°C for 30 minutes. The reaction mixture was cooled, filtered, and the filtrate evaporated in vacuo, the triturated with ether to give 48 mgs of racemic 1(S)-(1H-5-Imidazoyl)-2(R)-cyclopropyl-3-hydroxy-6-cyclohexyl-hexane and 1(R)-(1H-5-Imidazoyl)-2(S)-cyclopropyl-3-hydroxy-6-cyclohexyl-hexane.

NMR (CD_3OD, 300 MHz): d 8.8 (d, 1H), 7.37(m, 1H), 2.07 (m, 2H), 1.74 (m, 2H), 1.69(m, 1H), 1.55 (m, 1H), 1.44 (m, 1H), 1.32-1.10 (m, 13H), 0.87 (m, 2H). Mass Spectrum (DCI/NH_3); 263 $(M+1)^+$ MW=262.3974; $C_{16}H_{26}N_2O_1$.

EXAMPLES 20 AND 21

Preparation of 1(S)-[1H-5-imidazoyl]-2(R)-cyclopropyl-5(S)-amino-6-cyclohexyl-3-cis- hexene and 1(S)-[1H-5-imidazoyl]-2(R)-cyclopropyl-5(S)-amino-6-cyclohexyl-3-trans-hexene.



Step 1

3-cyclohexyl-1N-BOC-amino-propyl phenyl sulfone (3.4 grams, 9.2 mmoles) was dissolved in 150 ml of dry THF and cooled to -78°C under N_2. n-BuLi (2.5M, 7.3 ml,

18.3 mmoles) was added dropwise via syringe, and the reaction mixture stirred at -78°C for 1 hour. 3-[1-Triphenylmethyl-5-imidazoyl] -2-cyclopropylpropanal (3.5 grams, 9.2 mmoles) was dissolved in 100 ml of dry THF and added to the THF solution of sulfone anion slowly via syringe. After the addition was complete, the reaction was stirred for 1 hour. The reaction was quenched by the addition of a saturated solution of ammonium chloride (500 ml), and extracted with ethyl acetate (2X 150 ml). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford a viscous yellow oil. The crude product was purified by silica gel column chromatography using ethyl acetate/hexanes (3:7) to give 4.6 grams white solid, the racemic mixture of 1-[1-Triphenylmethyl-5-imidazoyl]cyclopropyl-3-hydroxy-4-phenylsulfonyl-5-(N-BOC)-amino-6-cylohexyl hexane.

Step 2.

1-[1-Triphenylmethyl-5-imidazoyl]cyclopropyl-3-hydroxy-4-phenylsulfonyl-5-(N-BOC)-amino-6-cylohexyl hexane (4.6 grams, 6.06 mmoles) was dissolved in dry methanol. Sodium hydrogen phosphate monobasic (6.02 grams, 42.4 mmoles) was added, and the reaction was cooled to 0°C under N_2. 2% Na(Hg) (2 portions of 15 grams) was added and the reaction mixture stirred for 1 hour. After that time, a second portion of Na(Hg) was added and the reaction stirred for an additional hour warming to r.t. The reaction mixture was filtered through a pad of celite, washing the pad with 100 cc of ethyl acetate. The filtrate was evaporated in vacuo, and the residue partitioned between CH_2Cl_2 and water (100:100 ml). The CH_2Cl_2 layer was separated, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified by column chromatography using ethyl acetate/hexanes (4:6) to give a white solid, 1-[1-Triphenylmethyl-5-imidazoyl]cyclopropyl-5-(N-BOC)-amino-6-cyclohexyl-3-hexene.

NMR ($CDCl_3$, 300 MHz): d: 7.30 (m, 9H), 7.12 (m, 7H), 6.58 (m, 1H), 6.53 (m, 1H), 5.40 (dd, 1H), 5.20 (m, 1H), 4.9 (m, 1H), 4.48 (m, 1H), 4.30 (m, 1H), 4.10 (m, 1H), 1.96 (m, 1H), 1.74 (m, 2H), 1.64 (m, 2H), 1.58 (s, 9H), 1.42 (s, 9H), 1.36-0.76 (m, 11H). NMR is of a 60:40 mixture of trans: cis olefins.

Step 3.

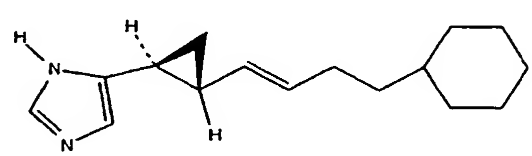
1-[1-Triphenylmethyl-5-imidazoyl]cyclopropyl-5-(N-BOC)-amino-6-cyclohexyl-3-hexene (1.87 grams, 3.1 mmoles) was dissolved in 15 cc of ethanol. 50 cc of 2N HCl was added and the mixture was heated at 90° C for 1 hour. The reaction mixture was cooled, filtered, and the filtrate neutralized with 10 % NaOH solution to pH 7-8. The

neutralized solution was evaporated in vacuo, and the residue partitioned between chloroform and water (100 ml each). The chloroform layer was separated, dried over sodium sulfate, filtered, and evaporated in vacuo to obtain a crude oil. The oil was purified using silica gel column chromatography using MeOH/Ethyl acetate/NH_4OH (9:90:1), to afford a pale yellow solid, 1(S)-[1H-5-imidazoyl]-(2R)-cyclopropyl-5-(S)-amino-6-cyclohexyl-3-trans-hexene and a yellow oil, 1(S)-[1H-5-imidazoyl]-(2R)-cyclopropyl-5-(S)-amino-6-cyclohexyl-3-cis-hexene.

NMR ($CDCl_3$, 300 MHz) Trans isomer: d 7.49 (s, 1H), 6.76 (s, 1H), 5.46 (dd, 1H), 5.20 (dd, 1H), 3.33 (q, 1H), 1.82 (m, 1H), 1.76- 1.56 (m, 6H), 1.36 - 1.12 (m, 8H), 0.98- 0.80 (m, 3H)
Cis Isomer: d 7.49 (s, 1H), 6.76 (s, 1H), 5.21 (t, 1H), 4.94 (t, 1H), 3.86 (q, 1H), 2.40- 1.96 (m, 5H), 1.86 (m, 2H), 1.68 (m, 4H), 1.40- 1.10 (m, 5H), 0.92 (m, 2H).

Mass Spectrum (DCI/NH_3): 260 $(M+1)^+$, MW= 259.3835, $C_{16} H_{25} N_3$.

EXAMPLE 22



Preparation of chiral 1-(S)-[1H-5-imidazoyl]-(2R)-cyclopropyl-6-cyclohexyl-3-trans-hexene

Chiral 1-(S)-[1H-5-imidazoyl]-(2R)-cyclopropyl-6-cyclohexyl-3-trans-hexene was prepared using compound 36 (See scheme XIII), 3-[1-Triphenylmethyl-5-imidazoyl]-2(R)-3(S)-cyclopropanoic butyl ester. The procedures used were the same as described for example 17.

Step 1

1(S)-[1-Triphenylmethyl-5-imidazoyl]-2(R)-cyclopropyl-3-hydroxy-4-phenylsulfonyl-6-cyclohexyl hexane (a diastereomeric mixture of hydroxy sulfones) (0.85 grams, 1.32 mmoles) was dissolved in 50 cc of dry methanol at 0°C. Sodium phosphate dibasic (1.30 grams) was added, followed by 11.30 grams of 2% Na(Hg). The reaction mixture was stirred for 1 hour at 0°C. The ice bath was removed, another 10

gram portion of 2% Na(Hg) was added, and the reaction mixture stirred for 1 hour at r.t. Finally, a third portion of 10 grams of 2% Na(Hg) was added, and the reaction stirred for 2 hours. The reaction mixture was filtered through a pad of celite, washing the pad with 50 cc of methanol, followed by 50 cc of ethyl acetate. The filtrate was evaporated in vacuo, and the residue partitioned between water (100 cc) and ethyl acetate (100 cc). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product obtained was purified by silica gel column chromatography using ethyl acetate/hexanes (1:9) to provide 485 mgs of a colorless viscous oil, a 1:1 mixture of 1(S)-[1-Triphenylmethyl-5-imidazoyl]-2(R)-cyclopropyl-6-cyclohexyl 3-trans hexene and 1(S)-[1-Triphenylmethyl-5-imidazoyl]-2(R)-cyclopropyl-6-cyclohexyl 3-cis hexene.

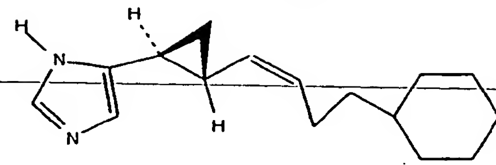
NMR ($CDCl_3$, 300 MHz): d 7.30 (m, 9H), 7.12 (m, 7H), 6.55 (br s, 1H), 6.52 (br s, 1H), 5.5 (m, 1H), 5.3 (m, 1H), 5.06 (m, 1H), 4.84 (m, 1H), 2.14 (m, 2H), 1.96 (m, 2H), 1.68 (m, 5H), 1.16 (m, 5H), 0.82 (m, 3H). NMR is of a 1:1 cis/trans mixture of geometrical isomers.

Step 2

The 1:1 mixture of 1(S)-[1-Triphenylmethyl-5-imidazoyl]-2(R)-cyclopropyl-6-cyclohexyl 3-trans hexene and 1(S)-[1-Triphenylmethyl-5-imidazoyl]-2(R)-cyclopropyl-6-cyclohexyl 3-cis hexene (0.475 grams) was dissolved in 3 cc of ethanol. 40 cc of 2N HCl was added, and the reaction mixture heated at 90°C for 1 hour. The reaction mixture was cooled, filtered, and neutralized with 10% sodium hydroxide solution to pH 7. The mixture was extracted with ethyl acetate (2X 100 cc), the ethyl acetate layer separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to afford a yellow viscous oil. The crude product was purified by silica gel column chromatography using ethyl acetate, and provided 66 mgs (less polar fraction) of a colorless glass, 1(S)-[1H-5-imidazoyl]-2(R)-cyclopropyl-6-cyclohexyl 3-cis hexene and 78 mgs of 1(S)-[1H-5-imidazoyl]-2(R)-cyclopropyl-6-cyclohexyl 3-trans hexene.

NMR ($CDCl_3$, 300 MHz): d 7.49 (d, 1H), 6.74 (d, 1H), 5.5 (dt, 1H), 5.08 (m, 1H), 2.90 (br s, 1H), 1.98 (m, 2H), 1.79 (m, 1H), 1.65 (m, 5H), 1.18 (m, 6H), 0.84 (m, 2H).

EXAMPLE 23

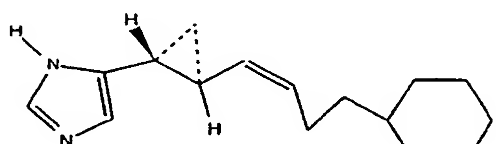


Preparation of chiral 1-(S)-[1H-5-imidazoyl]-(2R)-cyclopropyl-6-cyclohexyl-3-cis-hexene

See example 22 for the preparation of chiral 1-(S)-[1H-5-imidazoyl]-(2R)-cyclopropyl-5-(S)-amino-6-cyclohexyl-3-cis-hexene.

NMR ($CDCl_3$, 300 MHz): d 7.50 (d, 1H), 6.76 (d, 1H), 5.33 (dt, 1H), 4.86 (m, 1H), 2.90 (br s, 1H), 1.88 (m, 1H), 1.82 (m, 2H), 1.65 (m, 5H), 1.20 (m, 6H), 0.86 (m, 2H).

EXAMPLE 24



Preparation of chiral 1-(R)-[1H-5-imidazoyl]-2(S)-cyclopropyl-6-cyclohexyl-3-cis-hexene

Step 1

3-cyclohexylpropyltriphenylphosphonium iodide (3.6 grams, 6.9 mmoles) was suspended in 150 cc of dry THF and the mixture cooled to 0°C under N_2. $NaN(TMS)_2$ (1.0 M solution in THF, 6.9cc) was added dropwise via syringe, and the reaction was allowed to stir at 0°C for 1 hour. 3(R)-[1-Triphenylmethyl-5-imidazoyl]-2(S)-cyclopropylpropanal (1.7 grams, 4.5 mmoles) in 50 cc of dry THF was added dropwise (0.5 hour) to the ylide solution at 0°C. The reaction was stirred for 1 hour, quenched with 200 cc of a saturated solution of ammonium chloride, and extracted with ethyl acetate (2X 200 cc). The ethyl acetate layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a crude oil. The product was purified by silica gel column chromatography using CH_2Cl_2/ hexanes (1:1) followed by ethyl acetate/hexanes (3:7) to give 1.33 grams

of pale yellow foam, 1-(R)-[1-Triphenylmethyl-5-imidazoyl]-2(S)-cyclopropyl-6-cyclohexyl-3-cis-hexene.

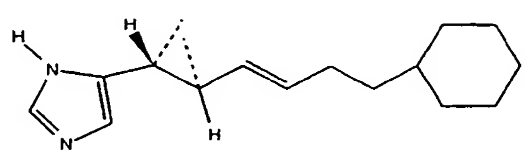
NMR($CDCl_3$, 300 MHz): d 7.30 (m, 9H), 7.26 (d, 1H), 7.12 (m, 6H), 6.55 (d, 1H), 2.14 (m, 1H), 1.92 (m, 1H), 1.76 (m, 2H), 1.64 (m, 5H), 1.20 (m, 6H), 0.82 (m, 2H).

Step 2

1-(R)-[1-Triphenylmethyl-5-imidazoyl]-2(S)-cyclopropyl-6-cyclohexyl-3-cis-hexene (1.33 grams) was dissolved in 4 cc of dry ethanol. 40 cc of 2N HCl was added, and the mixture heated at 90°C for 1 hour. The reaction mixture was cooled, filtered, and the filtrate neutralized with 10% NaOH to pH 7. The filtrate was extracted with ethyl acetate (2X 200 cc), the ethyl acetate layer separated, dried over $MgSO_4$, filtered, and evaporated in vacuo to give a yellow oil. Purification by silica gel column chromatography using ethyl acetate/hexanes (6:4) then ethyl acetate gave 488 mgs of a yellow oil, chiral 1-(R)-[1H-5-imidazoyl]-2(S)-cyclopropyl-6-cyclohexyl-3-cis-hexene.

NMR ($CDCl_3$, 300 MHz):d 7.50 (s, 1H), 6.78 (s, 1H), 5.34 (dt, 1H), 4.84 (m, 1H), 2.14 (m, 2H), 1.88 (m, 1H), 1.82 (m, 1H), 1.64 (m, 5H), 1.20 (m, 7H), 0.86 (m, 3H).

EXAMPLE 25

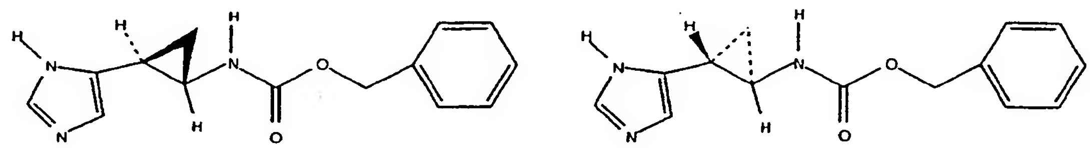


Preparation of chiral 1-(R)-[1H-5-imidazoyl]-2(S)-cyclopropyl-6-cyclohexyl-3-trans-hexene

Chiral 1-(R)-[1H-5-imidazoyl]-2(S)-cyclopropyl-6-cyclohexyl-3-trans-hexene was prepared using the procedures outlined in example 22.

NMR ($CDCl_3$, 300 MHz):d 7.48 (s, 1H), 6.74 (s, 1H), 5.52 (dt, 1H), 5.08 (m, 1H), 1.98 (m, 2H), 1.88 (m, 1H), 1.82 (m, 1H), 1.64 (m, 5H), 1.20 (m, 7H), 0.86 (m, 3H).

EXAMPLE 26

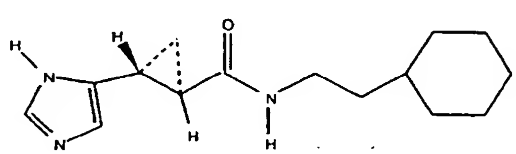


Preparation of racemic 1-(R)-[1H-5-imidazoyl]-2(S)-cyclopropylamine benzyl carbamate and 1-(S)-[1H-5-imidazoyl]-2(R)-cyclopropylamine benzyl carbamate.

Racemic 1-(R)-[1-Triphenylmethyl-5-imidazoyl]-2(S)-cyclopropylamine benzyl carbamate and 1-(S)-[1-Triphenylmethy-5-imidazoyl]-2(R)-cyclopropylamine benzyl carbamate were prepared as described in scheme XI. This racemate (235 mgs) was dissolved in 1 ml of $CHCl_3$ and added to 5 ml of 2N HCl. The reaction mixture was heated at 90°C for 45 minutes, cooled, filtered, and the filtrate concentrated in vacuo to dryness. Trituration with 2X 25 ml of ethyl acetate, collection of the solid by filtration, and drying under vacuum gave 110 mgs of racemic 1-(R)-[1H-5-imidazoyl]-2(S)-cyclopropylamine benzyl carbamate and 1-(S)-[1H-5-imidazoyl]-2(R)-cyclopropylamine benzyl carbamate.

NMR (CD_3OD, 300 MHz): d 8.85 (s, 1H), 8.80 (s,1H), 7.45 (s, 1H), 7.25 (s, 5H), 5.17 (s, 2H), 3.10 (m, 1H), 2.82 (m, 1H), 2.52 (m, 1H), 2.04 (m, 1H), 1.60 (m, 1H), 1.45 (m, 1H), 1.30 (m, 2H).

EXAMPLE 27



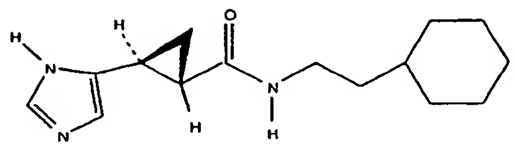
Preparation of N-[2-Cyclohexylethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide maleate salt

Chiral N-[2-Cyclohexylethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide maleate salt was made from 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-3(R)-cyclopropanoic butyl ester (37). The compound was prepared as described in example 1, except 2-cyclohexylethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.78 (s, 1H), 7.37 (s, 1H), 6.28 (s, 2H), 3.23 (m, 1H), 2.52 (m, 2H), 2.40 (m,1H), 1.97 (m, 3H), 1.72 (m, 4H), 1.62-1.18 (m, 6H), 0.94 (m, 2H).

Mass Spectrum (DCI/NH_3): 261 $(M+1)^+$, MW= 260.3612, $C_{15}\ H_{22}\ N_3\ O_1$

EXAMPLE 28



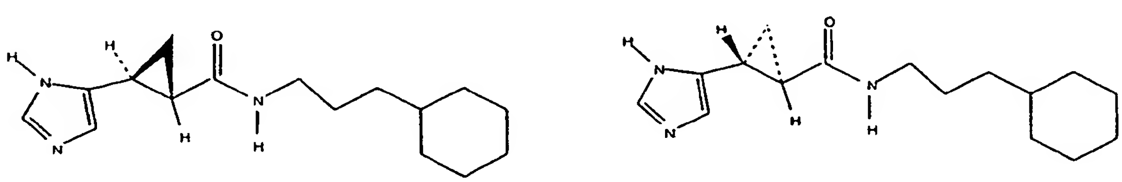
Preparation of N-[2-Cyclohexylethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide hydrochloride salt.

Chiral N-[2-Cyclohexylethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide hydrochloride salt was made from 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(R)-3(S)-cyclopropanoic butyl ester (37). The compound was prepared as described in example 1, except 2-cyclohexylethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.78 (s, 1H), 7.33 (s, 1H), 3.23 (m, 2H), 2.52 (m, 2H), 1.96 (m, 3H), 1.72 (m, 4H), 1.56-1.18 (m, 6H), 0.94 (m, 2H).

Mass Spectrum (DCI/NH_3): 261 $(M+1)^+$, MW= 260.3612, $C_{15}\ H_{22}\ N_3\ O_1$

EXAMPLE 29



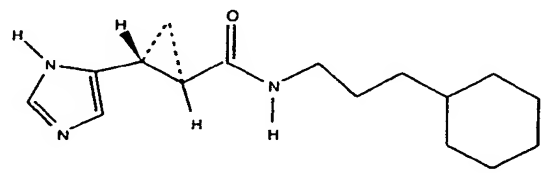
Preparation of racemic N-[3-Cyclohexylpropyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide and N-[3-Cyclohexylpropyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide

Racemic N-[3-Cyclohexylpropyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide and N-[3-Cyclohexylpropyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide were prepared as described in example 1, except 3-cyclohexylpropylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz):d 8.80 (d, 1H), 7.38 (d, 1H), 3.18 (m, 2H), 2.52 (m, 2H), 2.40 (m, 1H), 2.05 (m, 1H), 1.99 (m, 3H), 1.70 (m, 5H), 1.62-1.15 (m, 7H), 0.91 (m, 2H).

Mass Spectrum (DCI/NH_3): 276 $(M+1)^+$, MW= 275.3962, $C_{16}H_{25}N_3O_1$

EXAMPLE 30

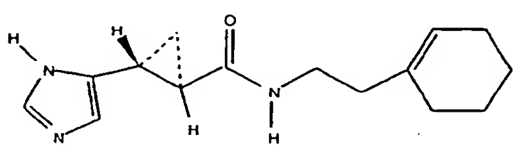


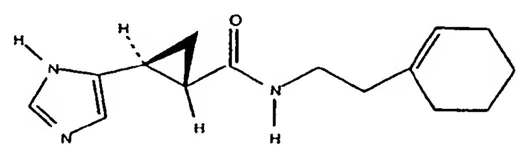
Preparation of chiral N-[3-Cyclohexylpropyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide.

Chiral N-[3-Cyclohexylpropyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide hydrochloride salt was made from 3-[(1-Triphenylmethyl-5-imidazoyl)]-2(S)-3(R)-cyclopropanoic butyl ester (36), and was prepared as described in example 1, except 3-cyclohexylpropylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz):d 8.74 (s, 1H), 7.30 (s, 1H), 3.16 (m, 2H), 2.40 (m, 1H), 1.92 (m, 1H), 1.70 (m, 6H), 1.55 (m, 4H), 1.25 (m, 7H), 0.91 (m, 2H).
Mass Spectrum (DCI/NH_3): 276 $(M+1)^+$, MW= 275.3962, $C_{16}H_{25}N_3O_1$

EXAMPLE 31





Preparation of racemic N-[2-Cyclohex-1-enyl-ethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[2-Cyclohex-1-enyl-ethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt

Racemic N-[2-Cyclohex-1-enyl-ethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[2-Cyclohex-1-enyl-ethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt were pepared as described in example 1, except 2-cyclohex-1-enyl-ethylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.9 (s, 1H), 7.55 (s, 1H), 5.60 (m, 1H), 3.70 (m, 2H), 3.0 (m, 4H), 2.30 (m, 1H), 2.20 (m,1H), 1.95 (m, 3H), 1.60 (m, 7H).
Mass Spectrum (DCI/NH_3): 260 $(M+1)^+$, MW= 259.3532, $C_{15}\, H_{21}\, N_3\, O_1$

EXAMPLE 32

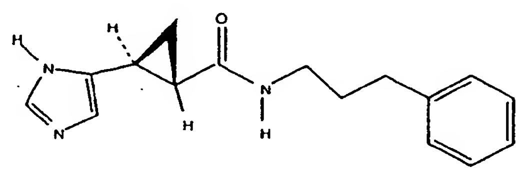
Preparation of racemic N-[1-cyclopropylmethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[1-cyclopropylmethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide. HCl salt

Racemic N-[1-cyclopropylmethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[1-cyclopropylmethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt were pepared as described in example 1, except (aminomethyl)cyclopropane was used instead of benzylamine.

NMR (CD_3OD, 300 MHz):d 8.80 (s, 1H), 7.38 (s, 1H), 3.0 (d, 1H), 2.80 (d, 1H), 2.40 (m, 1H), 1.98 (m, 1H), 1.50 (m, 1H), 1.32 (m, 1H), 0.98 (m, 1H), 0.50 (m, 2H), 0.20 (m, 2H).

Mass Spectrum (CDI/NH_3): 206 $(M+1)^+$, MW= 205.2612, $C_{11}\, H_{15}\, N_3\, O_1$

EXAMPLE 33

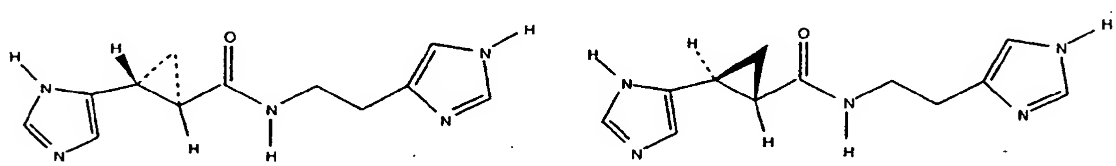


Preparation of racemic N-[3-Phenylpropyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[3-Phenylpropyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt

Racemic N-[3-Phenylpropyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[3-Phenylpropyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl $_{16}$salt were pepared as described in example 1, except 3-Phenylpropylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.78 (d, 1H), 7.34 (d, 1H), 7.22 (m, 5H), 3.22 (t, 2H), 2.92 (t, 1H), 2.72 (t, 2H), 2.64 (t, 2H), 2.40 (m, 1H), 1.96 (m, 1H), 1.83 (m, 1H), 1.52 (m,1H), 1.33 (m, 1H).
Mass Spectrum (DCI/NH_3): 270 $(M+1)^+$, MW= 269.3482,$C_{16}H_{19}N_2O_1$

EXAMPLE 34

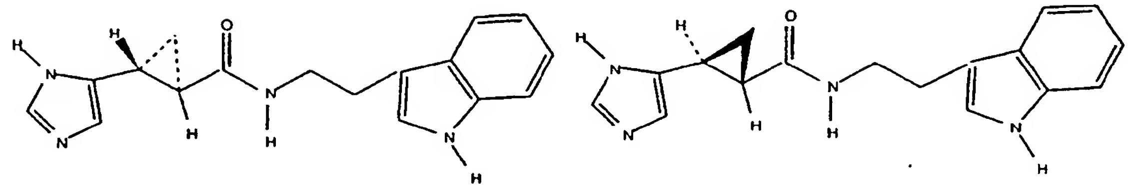


Preparation of racemic N-[2-(4)-imidazoylethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[2-(4)-imidazoylethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt

Racemic N-[2-(4)-imidazoylethyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[2-(4)-imidazoylethyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt were pepared as described in example 1, except N-[2-(4)-imidazoylethyl] amine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 8.82 (s, 1H), 8.79 (s, 1H), 7.39 (s, 1H), 7.36 (s, 1H), 3.54 (m, 2H), 3.30 (m, 1H), 2.94 (m, 1H), 2.40 (, 1H), 2.02 (m, 1H), 1.48 (m, 1H), 1.32 (m, 1H).

EXAMPLE 35

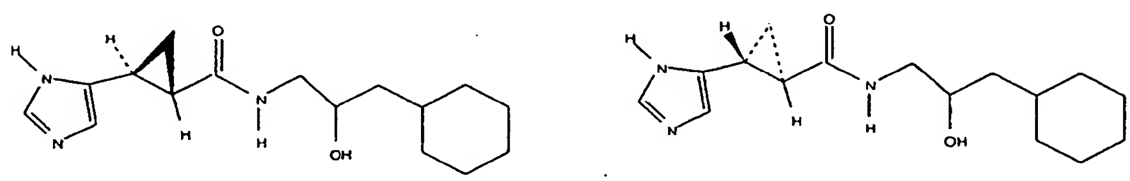


Preparation of racemic N-[3-(2-aminoethyl)indole]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[3-(2-aminoethyl)indole]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt

Racemic N-[3-(2-aminoethyl)indole]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide HCl salt and N-[3-(2-aminoethyl)indole]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide HCl salt were pepared as described in example 1, except N-[3-(2-aminoethyl)indole] was used instead of benzylamine.

NMR (CD_3OD, 300 MHz): d 7.55 (d, 1H), 7.52 (s, 1H), 7.31 (d, 1H), 7.06 (m, 2H), 6.96 (m, 1H), 6.84 (s, 1H), 3.48 (m, 2H), 3.30 (m, 2H), 2.95 (m, 2H), 2.32 (m, 1H), 1.80 (m, 1H), 1.38 (m, 1H), 1.20 (m, 1H).

EXAMPLE 36



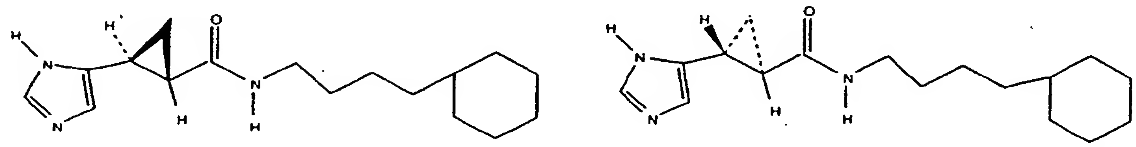
Preparation of racemic N-[3-Cyclohexyl-2-hydroxy-propyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide and N-[3-Cyclohexyl-2-hydroxy-propyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide hydrochloride salts

Racemic N-[3-Cyclohexyl-2-hydroxy-propyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide and N-[3-Cyclohexyl-2-hydroxy-propyl]-3(S)-[1H-5-imidazoyl]-

2(R)-cyclopropanamide were prepared as described in example 1, except 3-cyclohexyl-2-hydroxy-propylamine was used instead of benzylamine.

NMR (CD_3OD, 300 MHz):d 8.80 (d, 1H), 7.38 (d, 1H), 4.46 (d, 1H), 4.42 (d, 1H), 4.18 (d, 1H), 4.12 (d, 1H), 4.02 (m, 1H), 3.76 (d, 1H), 3.72 (d, 1H), 3.60 (m, 1H), 3.52 (m, 1H), 3.47 (t, 2H), 2.60 (m, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H), 1.96 (m, 1H), 1.70 (m, 5H), 1.62-1.15 (m, 7H), 0.91 (m, 2H).

EXAMPLE 37



Preparation of racemic N-[4-Cyclohexylbutyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide and N-[4-Cyclohexylbutyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide hydrochloride salts

Racemic N-[4-Cyclohexylbutyl]-3(R)-[1H-5-imidazoyl]-2(S)-cyclopropanamide and N-[4-Cyclohexylbutyl]-3(S)-[1H-5-imidazoyl]-2(R)-cyclopropanamide were prepared as described in example 1, except 4-Cyclohexylbutylamine was used instead of benzylamine.

NMR (CD_3Cl, 300 MHz): d 8.00 (s, 1H), 6.62 (s, 1H), 5.65 (m, 1H), 3.44 (m, 1H), 3.22 (m, 1H), 2.68 (t, 1H), 2.30 (m, 1H), 2.0 (m, 1H),1.78 (m, 2H), 1.66 (m, 4H), 1.42 (m, 2H), 1.20 (m, 6H), 0.82 (m, 2H).

The compounds of this invention are antagonists of the histamine H_3 receptor. The binding affinity of the compounds of the invention to the H_3 receptor may be demonstrated by the procedure described below:

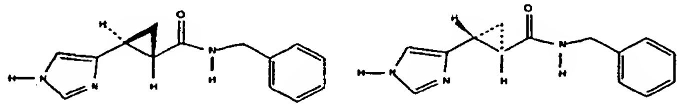
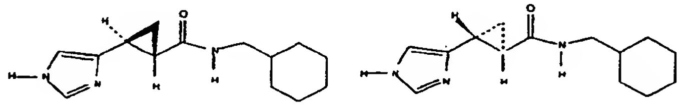
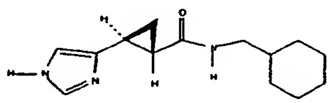
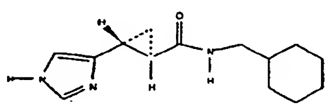
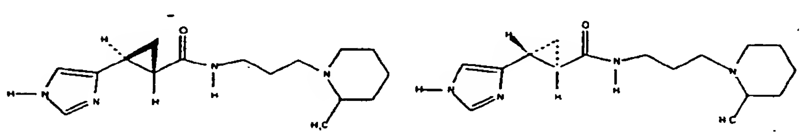
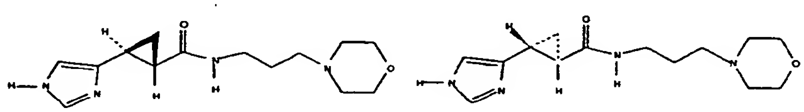
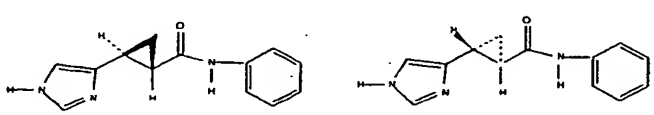
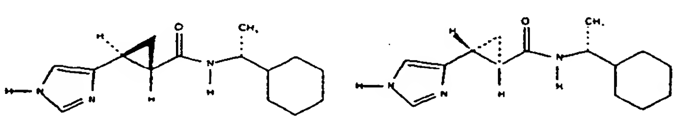
In Vitro Histamine H_3 Receptor Binding Analysis.

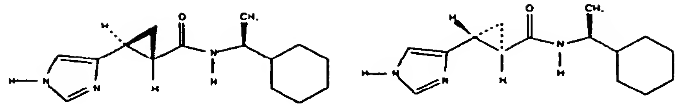
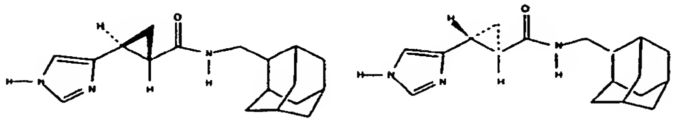
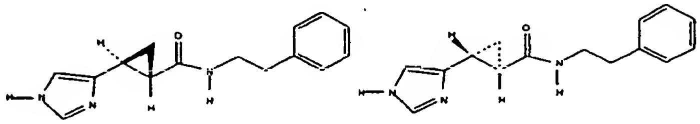
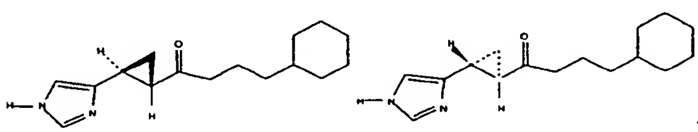
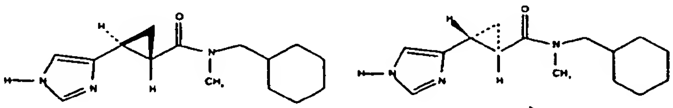
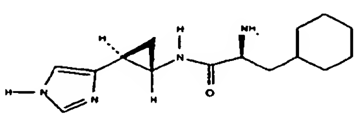
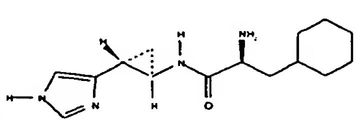
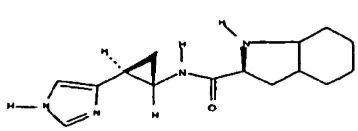
Histamine H_3 receptor affinity was determined in rat cortical membranes using the H_3 selective agonist ligand, $[^3H]$-N^{α}-methylhistamine (78.9 Ci/mmole, DuPont NEN Research Products, Boston, MA) according to the method of West et al., (1990) *Mol. Pharmacol.* 38: 610-613 with modifications. Briefly, animals were sacrificed by decapitation and the cerebral cortex was rapidly removed. Rat cortices were mechanically homogenized with an Omni 1000 motor driven homogenizer in 10 volumes (wt/vol) of Krebs-Ringers Hepes buffer (pH 7.4) containing the following protease inhibitors; EDTA (10 mM), PMSF (0.1mM), chymostatin (0.2 mg/50mL) and leupeptin (0.2 mg/50mL). The homogenate was centrifuged in a Sorvall at ~40,000 x g for 30 min. The pellet was resuspended by mechanical homogenization in 25 mL water and lysed on ice for 30 min. The homogenate was recentrifuged and the membrane lysis was repeated. The membranes were recentrifuged and the final pellet was resuspended in 14 volumes of water to give approximately 200 µg protein/100 µl final concentration. The suspension was stored at -80°C prior to use. Protein concentrations were determined by Coomassie Plus Protein Assay (Pierce, Rockford, IL).

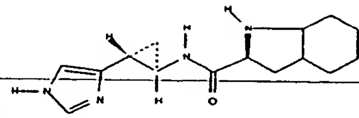
The binding assay was carried out in polypropylene tubes in a total volume of 0.4 ml of 50 mM Na^+ Phosphate buffer (pH 7.4), containing 150-200 µg of tissue protein, 0.8-1.2 nM $[^3H]$-N^{α}-methylhistamine and 0.3 to 10,000 nM GT-2016. Nonspecific binding (NSB) was accounted for by the inclusion of thioperamide (10 µM). Samples were incubated for 40 minutes at 25°C. The samples were filtered through glass fiber strips, pre-washed with 0.3% polyethyleneimine, using a Brandell cell harvester. The filters were rapidly washed three times with 4 ml of 25 mm Tris buffer containing 145 mM NaCl (pH 7.4, 4°C). Filters were transferred to polyethylene minivials and counted in 3.5 ml of scintillation fluid (Ecolume, ICN Biomedicals, Inc.). Using this procedure, the non-specific binding was less than 10% of the total binding and the binding to the glass fiber filters was negligible. Saturation and competition experiments were analyzed with the ReceptorFit saturation and competition curve fittingprograms (Lundon Software, Inc., Cleveland, OH). K_i's were determined using the equation $K_i = IC_{50}/(1 + ([\text{Ligand}]/[K_d]))$. The results are given in Table 1.

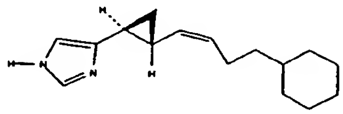
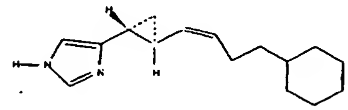
TABLE 1

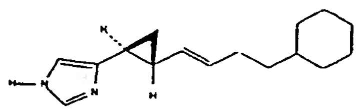
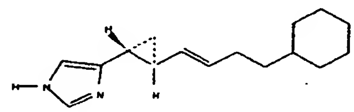
Histamine H$_3$ Receptor Binding Affinities

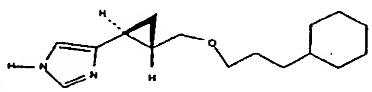
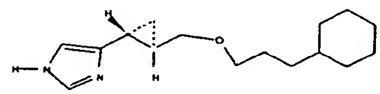
Compound	Structure	H$_3$ Receptor K$_i$ (nM)
Example 1		53 ±2
Example 2		37 ±4
Example 2a		23 ±1
Example 2b		176 ±9
Example 3		659 ±52
Example 4		1402±158
Example 5		267 ±26
Example 6		70 ±8.6

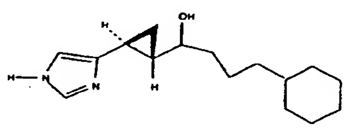
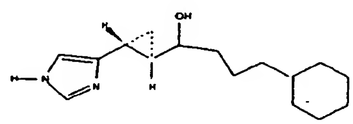
Example 7		146 ±13
Example 8		55 ±6
Example 9		163 ±19
Example 10		97 ±21
Example 11		134 ±13
Example 12		1.85±0.5
Example 13		21.5 ± 1.8
Example 14		8.5± 0.7

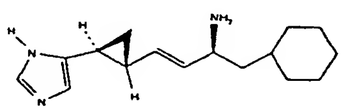
Example 15  37 ± 4

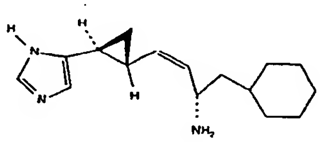
Example 16   12.2 ±1.0

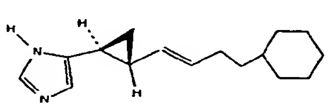
Example 17   11.0 ±1.0

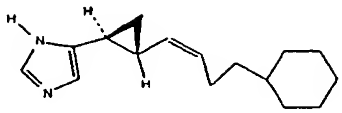
Example 18   240 ±6.0

Example 19   160 ±9.0

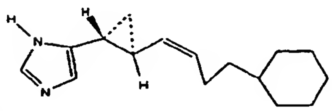
Example 20  0.37 ±0.2

Example 21  97.7 ±28

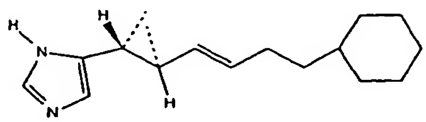
Example 22  2.4 ±0.2



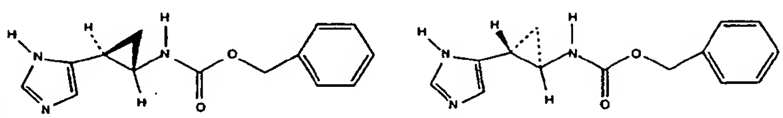
Example 23 6.2 ±0.8



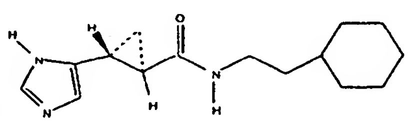
Example 24 108 ±3.9



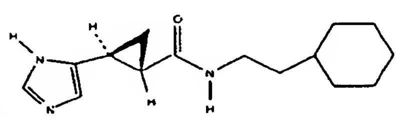
Example 25 56 ±9.0



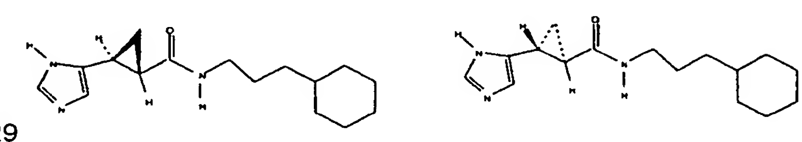
Example 26 5.8 ±0.4



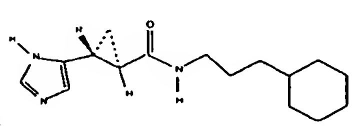
Example 27 8.8 ±0.1



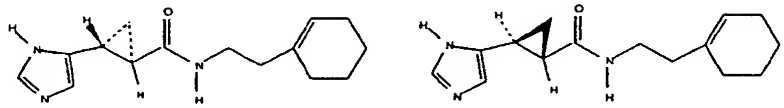
Example 28 46 ±1 3



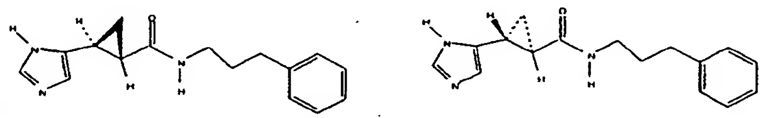
Example 29 36 ±8.0

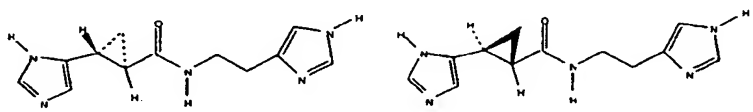


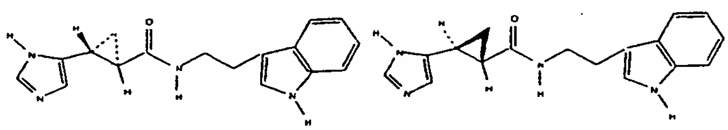
Example 30 42 ±7.0

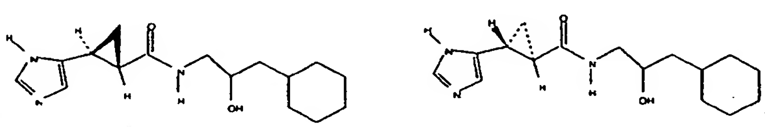
Example 31  294 ±26

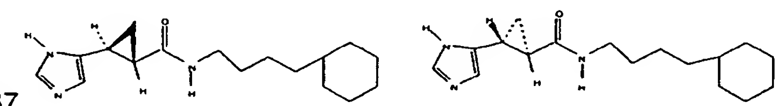
Example 32  876 ±158

Example 33  197 ±23

Example 34  227 ±26

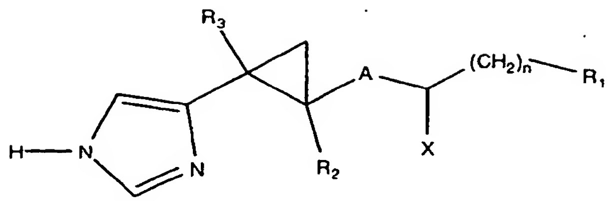
Example 35  441 ±73

Example 36  145

Example 37  68 ±9.1

WHAT IS CLAIMED IS:

1. A compound of the formula:



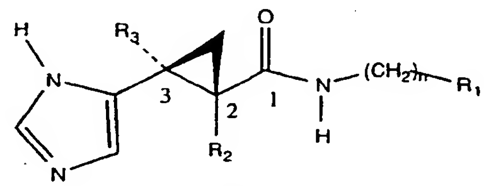
(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

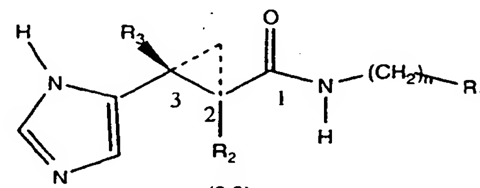
R_2 is a hydrogen or a methyl or ethyl group;
R_3 is a hydrogen or a methyl or ethyl group;
n is 0, 1, 2, 3, 4, 5, or 6; and
R_1 is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (c) alkyl; (d) heterocyclic; (e) decahydronapthalene; and (f) octahydroindene;
with the provisos that
when X is H, A can be $-CH_2CH_2-$, $-COCH_2-$, -CONH-, $-CON(CH_3)-$, -CH=CH-, $-C\equiv C-$, $-CH_2-NH-$, $-CH_2-N(CH_3)-$, $-CH(OH)CH_2-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-CH_2O-$, $-CH_2S-$, or -NHCOO-;

when X is NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, CH_3, SH, or SCH_3; A can be -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or $-C\equiv C-$; and
when R_1 and X taken together denote a 5,6 or 6,6 saturated bicyclic ring structure X can be NH, O, or S.

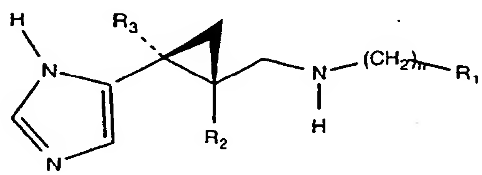
2. A compound or a pharmaceutically acceptable salt or solvate thereof, as in claim 1 selected from the group consisting of:



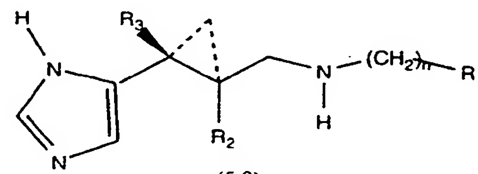
(2.0)



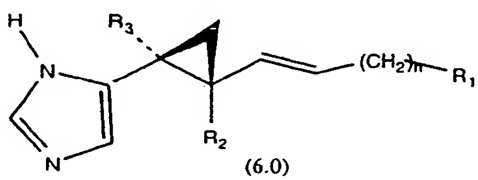
(3.0)



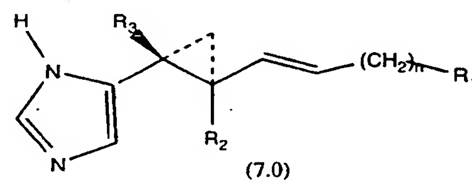
(4.0)



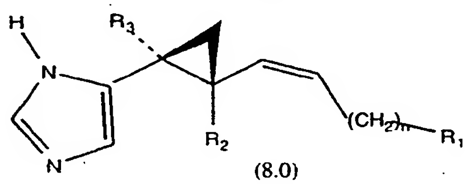
(5.0)



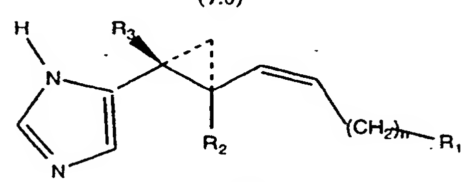
(6.0)



(7.0)



(8.0)



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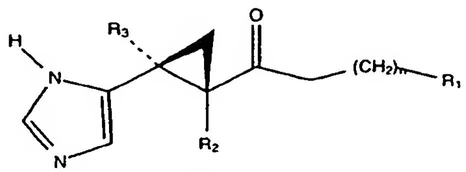
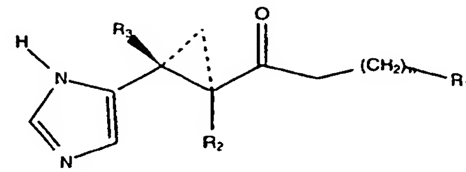
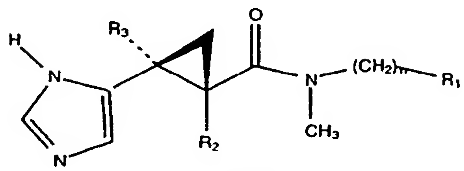


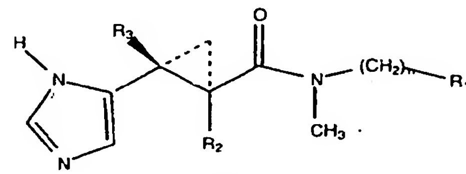
(10.0)



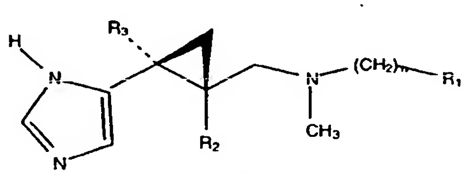
(11.0)



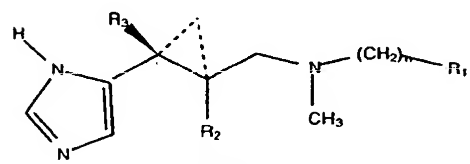
(12.0)



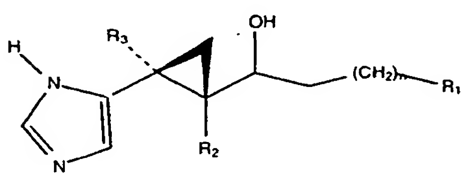
(13.0)



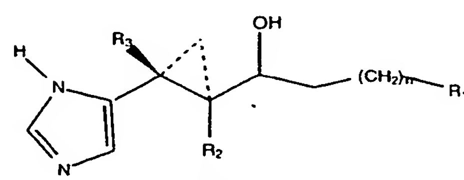
(14.0)



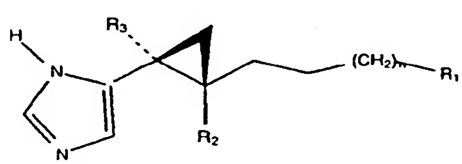
(15.0)



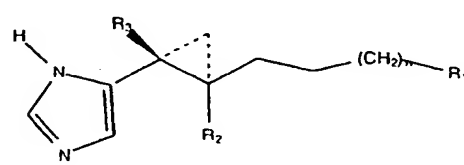
(16.0)



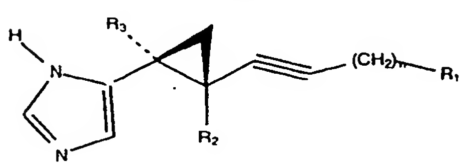
(17.0)



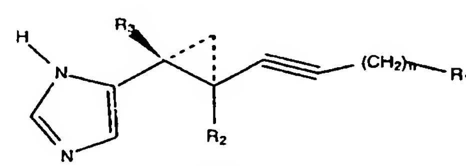
(18.0)



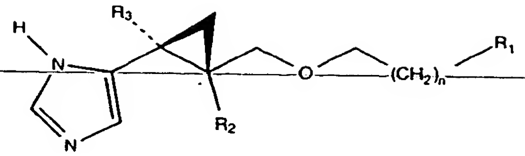
(19.0)



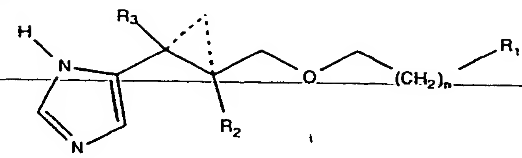
(20.0)



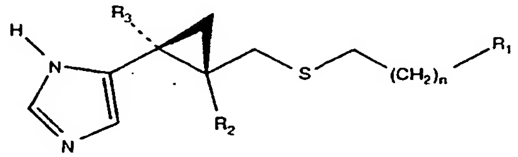
(21.0)



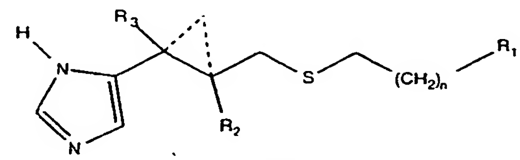
(22.0)



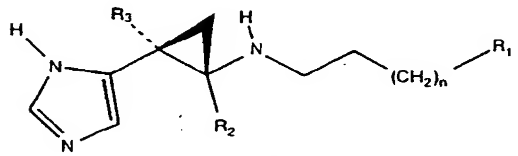
(23.0)



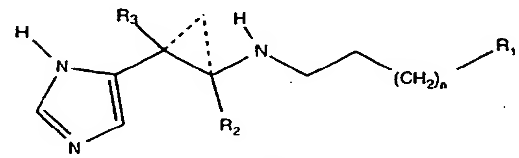
(24.0)



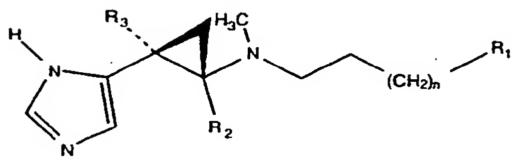
(25.0)



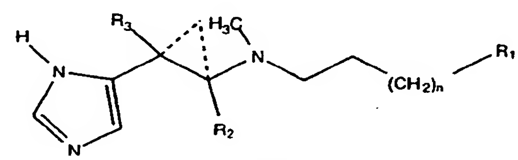
(26.0)



(27.0)



(28.0)



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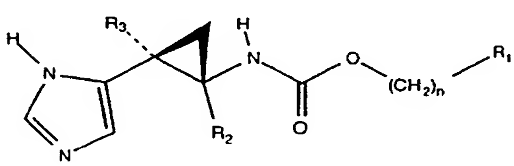

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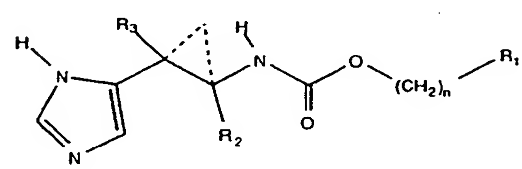

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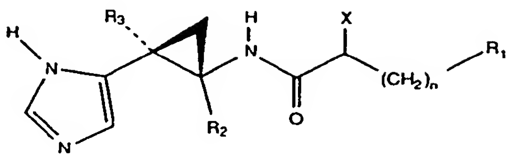

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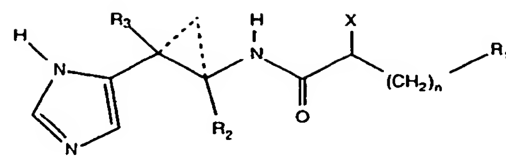

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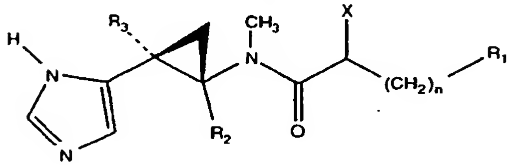

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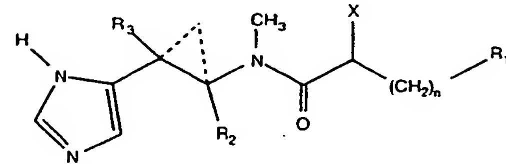

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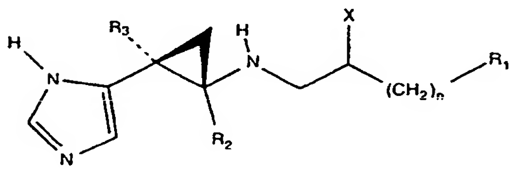
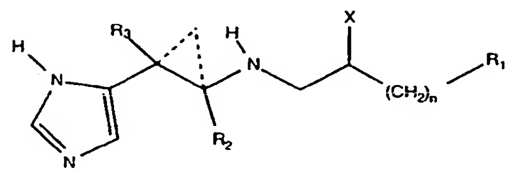


(36.0)



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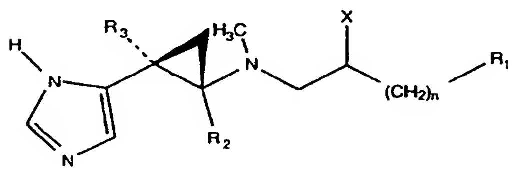
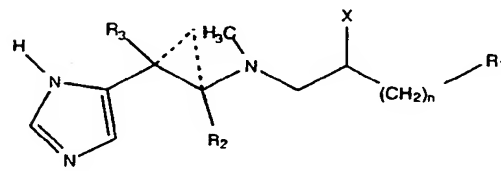


(38.0)



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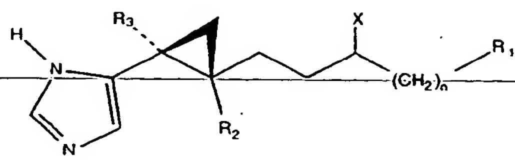

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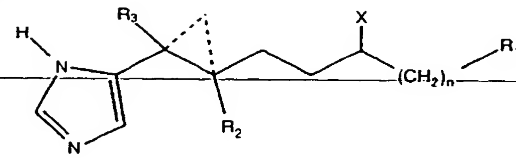

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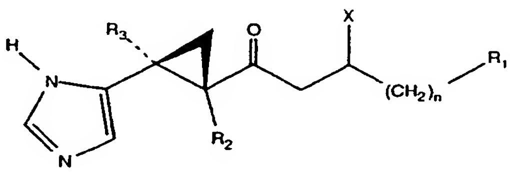

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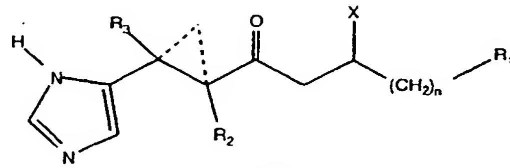
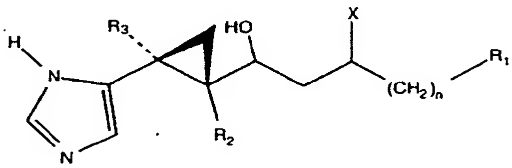
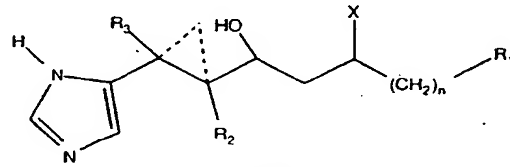


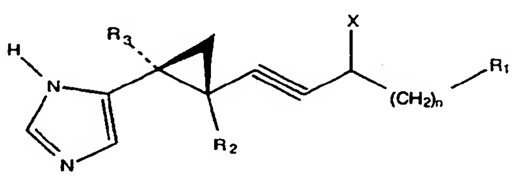
(43.0)



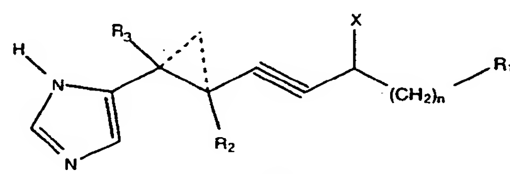
(44.0)



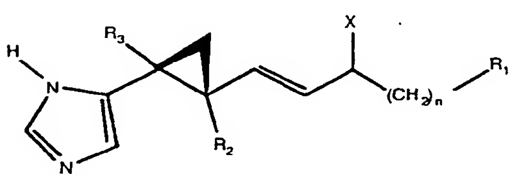
(45.0)



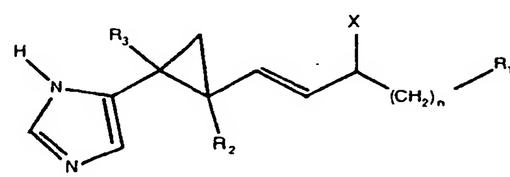
(46.0)



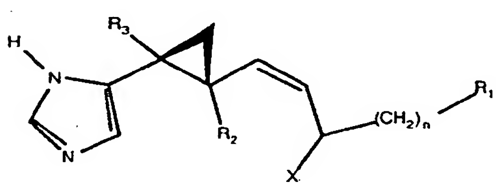
(47.0)



(48.0)

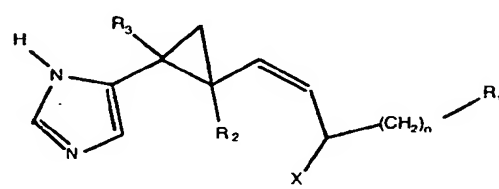


(49.0)



(50.0)

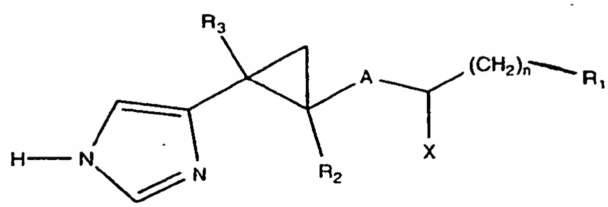
and



(51.0)

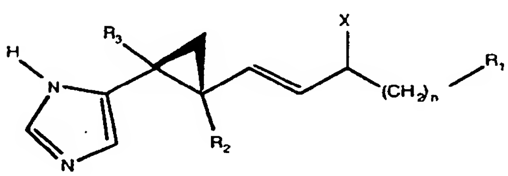
wherein R_1, R_2, R_3 X and n are as defined in claim 1.

3. A compound of the formula :

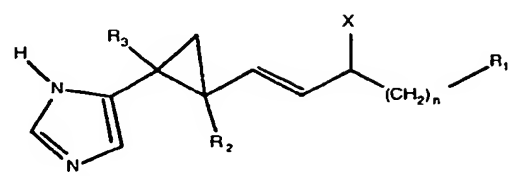


or a pharmaceutically acceptable salt or hydrate thereof, where A is -CONH, -CH=CH-, -NHCOO-, or $-C\equiv C-$;
X is H, CH_3 or NH_2 ;
R_2 and R_3 are H;
n is 0, 1, 2 or 3; and
R_1 is C_6 cyclohexyl, phenyl or substituted phenyl.

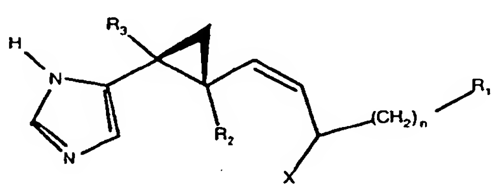
4. A compound as in claim 3 having the formula:



(48.0)

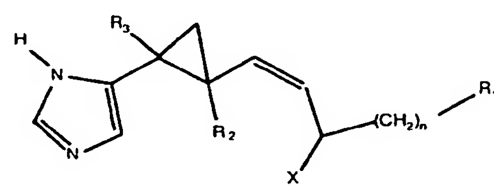


(49.0)



(50.0)

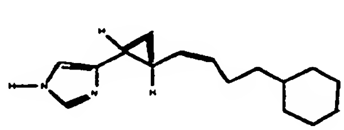
or



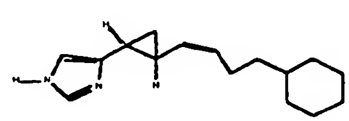
(51.0)

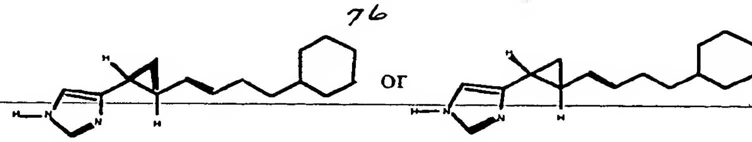
wherein R_1, R_2, R_3, X and n are defined as in claim 3.

5. A compound as in claim 4 having the structure:



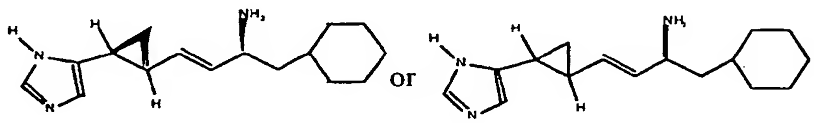
or





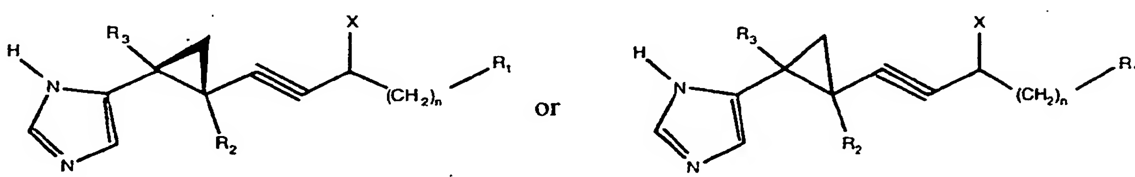
or a pharmaceutically acceptable salt therof.

6. A compound as in claim 4 having the structure:



or a pharmaceutically acceptable salt therof.

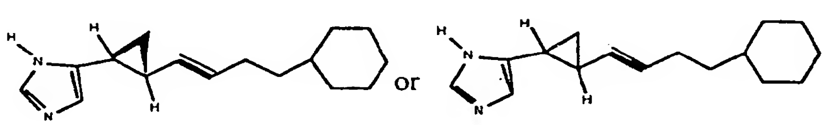
7. A compound as in claim 3 having the formula:



(46.0) (47.0)

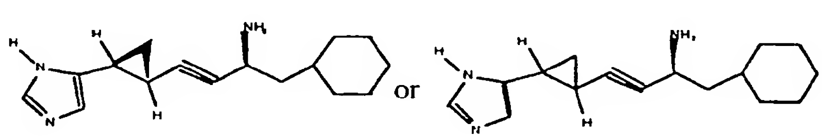
wherein R_1, R_2, R_3, X and n are defined as in claim 3.

8. A compound as in claim 7 having the structure:



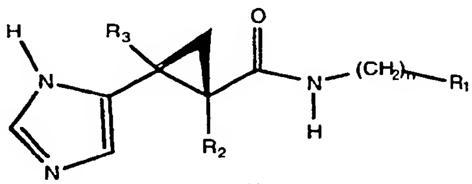
or a pharmaceutically acceptable salt therof.

9. A compound as in claim 7 having the structure:



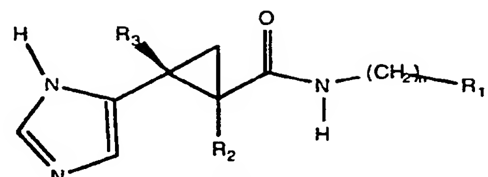
or a pharmaceutically acceptable salt therof.

10. A compound as in claim 3 having the formula:



(2.0)

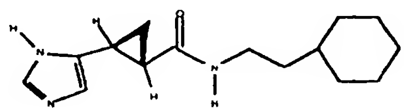
or



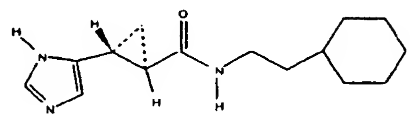
(3.0)

wherein R_1, R_2, R_3 and n are defined as in claim 3.

11. A compound as in claim 10 having the structure:

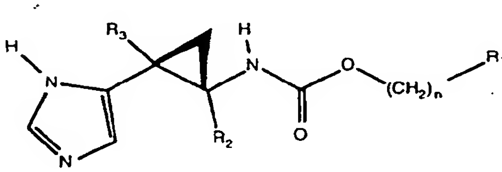


or



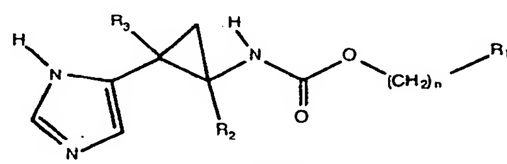
or a pharmaceutically acceptable salt therof.

12. A compound as in claim 3 having the formula:



(30.0)

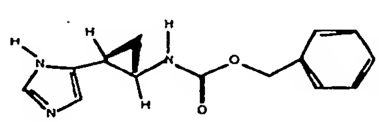
or



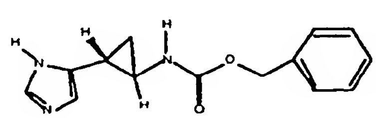
(31.0)

wherein R_1, R_2, R_3 and n are defined as in claim 3.

13. A compound as in claim 12 having the structure:



or



or a pharmaceutically acceptable salt therof.

14. A pharmaceutical composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier.

15. A method of preparing a pharmaceutical composition comprising admixing a compound of claim 1 with a pharmaceutically acceptable carrier.

16. A method of treating allergy, inflammation, cardiovascular disease (i.e. hyper or hypotension), gastrointestinal disorders (acid secretion, motility) and CNS disorders involving attention or cognitive disorders, (i.e., Alzheimer's, Attention Deficit Hyperactive Disorder, age-related memor dysfunction, stroke, etc.), CNS psychiatric disorders and motor disorders (i.e., depression, schizophrenia, obsessive-compulsive disorders, tourette's syndrome, etc.), sleep disorders (i.e. narcolepsy, sleep apnea, insomnia, disturbed biological and circadian rhythms, hyper and hyposomnolence, and related sleep disorders), epilepsy, hypothalamic dysfunction (i.e., eating disorders such as obesity, anorexia/bulimia, thermoregulation, hormone release) comprising administering an effective amount of a compound of claim 1 to a patient in need of such treatment.

17. A method of antagonizing histamine H_3 receptors comprising administering to said H_3 receptors an effective amount of at least one compound of claim 1.

18. A method of preparing a pharmaceutical composition comprising admixing at least one compound of Claim 1 with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07833

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/415; C07D 233/60
US CL :514/400; 548/338.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/400; 548/338.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,217,986A (POMPONI ET AL.) 08 June 1993, see entire document.	1-16 and 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 AUGUST 1996	03 SEP 1996

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	PATRICIA MORRIS jd
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07833

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1-15 and 18, drawn to compounds, compositions and process of preparing, classified in Class 548, subclass 335.1
Claim 16, drawn to a method of treating allergy, classified in Class 514, various subclasses.
II. Claims 16, drawn to a method of treating inflammation, classified in Class 514, various subclasses.
III. Claim 16, drawn to a method of treating cardiovascular disease, classified in Class 514, various subclasses.
IV. Claim 6, drawn to a method of treating CNS psychiatric disorders, classified in Class 514, various subclasses.
V. Claim 16, drawn to a method of treating CNS psychiatric disorders and motor disorder and motor disorders, classified in Class 514, various subclasses.
VI. Claim 16, drawn to a method of treating sleep disorders, classified in Class 514, various subclasses.
VII. Claim 16, drawn to a method of treating epilepsy, classified in Class 514, various subclasses.
VIII. Claim 16, drawn to a method of treating hypothalamic dysfunction, classified in Class 514, various subclasses.
IX. Claim 17, drawn to a method of antagonizing histamine H3 receptors, classified in Class 514, various subclasses.
X. Claim 16, drawn to a method of treating gastrointestinal disorders, classified in Class 514, various subclasses.

The inventions listed as Groups I-IX do not meet the requirements for Unity as Invention because Groups II-I are drawnto multiple methods of use that are distinct treatment of physiologic disorder and separately classified > In accordance with PCT Rule 13.2 claims are permitted to one product, one process of manufacturing and one use.